FRAILTY SCREENING AND IMPAIRMENT PATTERNS IN OLDER ADULTS WITH CANCER: A DISSERTATION USING THE CANCER AGING AND RESILIENCE EVALUATION (CARE) REGISTRY

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A dissertation submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Epidemiology (Pharmacoepidemiology) in the Gillings School of Global Public Health.

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ABSTRACT

Sydney Thomas Thai: Frailty Screening and Impairment Patterns in Older Adults with Cancer: A Dissertation Using the Cancer Aging and Resilience Evaluation (CARE) Registry
(Under the direction of Jennifer L. Lund)

Older adults with cancer often have multiple health impairments.[1-3] Although geriatric assessments are recommended to identify older adult impairments not captured in oncology assessments, impairments are not often evaluated.[1,4,5] Thus, patients may undergo treatment without support for impairments associated with adverse outcomes. The objectives were to evaluate the screening performance of skeletal muscle density (SMD) in classifying frailty in older adults with cancer (Aim 1) and to identify and describe geriatric assessment impairment patterns in older adults with gastrointestinal cancers (Aim 2).

We used the Cancer Aging and Resilience Evaluation (CARE) registry (University of Alabama at Birmingham). Patients completed the CARE tool, a self-reported geriatric assessment, and responses were used to calculate frailty scores and categorize impairment indicators.[6-9] SMD was calculated from computed tomography scans (L3 vertebrae), and performance in classifying frailty was evaluated using diagnostic model methods and compared by gender-diabetes status. Using latent class analysis (LCA) with impairment indicators, we identified impairment classes among patients with gastrointestinal malignancies and described classes using impairment probabilities, patient characteristics, and one-year mortality.

SMD performed poorly. Area under the receiver operating curve (AUC) estimates were low for all four gender-diabetes subsets (range: 0.58-0.68). Third quartile gender-specific cut-off points for SMD had high sensitivity (0.76-0.89), but low specificity (0.25-0.34). Positive and

negative likelihood ratio results indicated that utility was most promising for men with diabetes compared to other subgroups.

We identified 6 impairment latent classes (LC): mild impairment (LC1, 28% prevalence); social support impairment (LC2, 12%); weight loss alone (LC3, 16%); impaired, low anxiety/depression (LC4, 23%); impaired with anxiety/depression (LC5, 11%); global impairment (LC6, 11%). One-year mortality risk estimates ranged from 11% (mild impairment) to 44% (global impairment) compared to 14-34% when using frailty categories. In overall and stratified analyses (high- vs. low-risk cancers), mortality estimates for the 3 impaired classes (LC4, LC5, LC6) were greater than the mild impairment class.

Work is needed to improve classification of frailty with SMD and to assess performance in other subgroups and populations. The identified geriatric assessment impairment classes can facilitate awareness of impairment clustering and the planning of support services for older adults with cancer.

For my parents, Huu and MyThuong, and siblings Chris and Kathleen.
And for the patients, nursing staff, and research staff of the CARE Registry.

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.

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LIST OF ABBREVIATIONS

aBIC = Adjusted Bayesian information criterion

AIC = Akaike information criteria

ADL / ADLs = Activities of daily living

ARIC = Atherosclerosis Risk in Communities (Study)

ASCO = American Society of Clinical Oncology

AUC = Area under the receiver operating characteristic curve

BLRT = Bootstrap likelihood ratio tests

BIC = Bayesian information criteria

BMI = Body mass index

BSA = Body Surface Area

CARE = Cancer and Aging Resilience Evaluation

CARG = Cancer and Aging Research Group

CGA = Comprehensive Geriatric Assessment

CI = Confidence interval

CT = Computed tomography

ECOG = Eastern Cooperative Oncology Group

ECOG-PS = Eastern Cooperative Oncology Group Performance Status (scale)

FPF = False-positive fraction

FPG = Fasting plasma glucose

GA = Geriatric assessment

GEE = generalized estimating equation

GIST = Gastrointestinal stromal tumors

Health ABC = Health, Aging and Body Composition (study)

HbA1c = Hemoglobin A1c

HR = Hazard ratio

HRQOL = Health-related quality of life

HU = Hounsfield units

IADL / IADLs = Instrumental activities of daily living

IMAC = Intramuscular adipose tissue content

IQR = Interquartile range

IRB = Institutional review board

Kcals = Kilocalories

L3 = Third lumbar vertebra

LC = Latent Class

LR+ = Positive likelihood ratio

LR- = Negative likelihood ratio

LRT = Likelihood ratio tests

MA = Muscle attenuation

MMSE = Mini-Mental State Examination

MNA = Mini-Nutritional Assessment

MOS = Medical Outcomes Safety

MRI = Magnetic resonance imaging

NCDB = National Cancer Data Base

NHANES = National Health and Nutrition Examination Survey

NPV = Negative predictive value

OARS = Older Americans and Services

OR = Odds Ratio

PFP = Physical frailty phenotype

PPV = Positive predictive value

PR = Prevalence ratio

Pr = Probability (in equations)

PROMIS = Patient-Reported Outcomes Measurement Information System

Q1 = first quartile

Q3 = third quartile

RD = Risk difference

RR = Risk ratio

ROC = Receiver operating characteristics (curve)

SEER = Surveillance, Epidemiology, and End Results (Program)

SIOG = International Society of Geriatric Oncology

SMD = Skeletal muscle density

SMI = Skeletal muscle index

T4 = Fourth thoracic vertebra

TPF = True-positive fraction

UAB = University of Alabama at Birmingham

VES-13 = Vulnerable Elders Survey 13 (VES-13)

WHAS = Women's Health and Aging Study

CHAPTER 1: SPECIFIC AIMS

Frailty is a biologic syndrome characterized by a decreased reserve and resistance to stressors. For older adults, it confers an increased vulnerability to adverse outcomes (e.g., falls, institutionalization, mortality).[10-14] Among older adults with cancer, **the burden of frailty is high** with one systematic review reporting frailty prevalence ranging from 43-64% among cancer studies using ≥2 deficits to define frailty.[2] Among older patients newly treated with chemotherapies, there is evidence that **frailty markers (e.g., hand grip strength) may be associated with 3-month risk of treatment toxicities among survivors**.[15] In acknowledging that older adult patients are a heterogenous population with differences in accrued comorbid conditions, disabilities, and health deficits, the American Society of Clinical Oncology (ASCO) recommends geriatric assessment to identify impairments that are not regularly captured in oncology assessments. Unfortunately, these **clinical evaluations are reportedly underutilized in older adults starting cancer therapy**.

Previous research has proposed the use of computed-tomography-derived muscle metrics to screen for frailty, and efforts have been made to understand impairment patterns that contribute to frailty. Skeletal muscle density (SMD) is an indirect indicator of excessive adipose infiltration into muscle tissue—a pathological phenomenon termed myosteatosis— and low SMD has been shown to be associated with hospitalizations and chemotherapy toxicities.[16] However, SMD performance for classifying frailty in older adults with cancer has not been evaluated, and performance evaluation based on sex and diabetes is warranted due to documented differences in how intermuscular fat may accrue in these older adult subgroups.[17] Additionally, one previous study attempted to describe impairment patterns in older adults with cancer. However, the authors

omitted several domains that are evaluated in a geriatric assessment and the inclusion of multiple cancer types may be not be informative for patients with gastrointestinal cancer for which treatment modalities and patient characteristics may differ from other cancers.

This dissertation work will evaluate the screening performance of SMD in classifying frailty and describe impairment patterns that may be seen in older adults with cancer. The aims will leverage data from the Cancer & Aging Resilience Evaluation (CARE) Registry, an ongoing single-site registry of older adult patients with predominantly late-stage and gastrointestinal cancers. Most of these patients have baseline imaging and clinical measurements before the start of cancer treatment. Frailty and geriatric impairments are evaluated using a completely patient-reported geriatric assessment that is completed at the time of registry enrollment. This study will address the following aims:

Aim 1. Assess the performance of SMD as a screening tool for frailty in older adults with cancer. **(1.1.)** Compare performance between men and women with and without comorbid diabetes. **(1.2.)** Evaluate the clinical utility of positive and negative SMD results on predictions of patient frailty.

Aim 2. Identify and describe impairment pattern profiles in patients with gastrointestinal malignancies.

Public health impact. This research expands upon current knowledge on frailty screening using skeletal muscle composition, and findings will help elucidate impairment profiles of older adults who are starting chemotherapy. Both aims will further our understanding of frailty, and results may inform interventions aimed at identifying vulnerable patients for risk stratification and treatment decision making and planning support care for older adults undergoing cancer treatment.

CHAPTER 2: BACKGROUND AND SIGNIFICANCE

2.1. Frailty

2.1.1. Frailty Conceptualizations for Medicine

In medical practice, the term “frailty” is often used to characterize the weakest and most vulnerable subset of patients.[18] Unlike specific diseases that a clinician may have been trained to identify, frailty is almost never the basis for a “chief complaint”, and its manifestations may be subtle or asymptomatic.[19] While there are many conceptualizations and definitions of frailty, consensus expert opinion has acknowledged that physical frailty is a specific medical syndrome within the broader context of frailty.[20] Based on this consensus, frailty, as it pertains to physical frailty, is defined as:

> *…a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual’s vulnerability for developing increased dependency and/or death.* (2012 Frailty Consensus Conference, Orlando Florida).[20]

Broader constructs of frailty additionally incorporate frailty as a state of increased vulnerability due to accrued impairments in multiple body systems; this state confers a diminished ability to respond to even mild stresses.[20,21] As a syndrome, manifestations of frailty contributors may occur in combination, and no single clinical manifestation sufficiently identifies patients with the syndrome.[18] As a multi-faceted and common condition, physical frailty is similar to multimorbidity. However, multimorbidity is more prevalent in older and younger adults (89-95% for older adults; 68-74% for adults 45 to 64 years), and there is a notable difference based on management.[20,22] While multimorbidity treatment focuses on managing each condition separately, physical frailty is treated by applying a general treatment approach to address specific health areas.

Frailty is also similar but distinct from sarcopenia and cachexia. All three conditions are characterized by losses in muscle mass, strength, and function.[23,24] In sarcopenia, the loss of muscle mass is attributed to aging and normal physiological change; and there is slow, largely irreversible, declines in muscle mass and strength that affect daily living activities.[24,25] Cachexia meanwhile is considered a "metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass."[26] Weight loss is a prominent clinical feature of cachexia in adults; and patients also commonly experience anorexia, inflammation, insulin resistance, and increased muscle protein breakdown. **Table 1** summarizes features of these three conditions. In cross-sectional analyses, frail older adults have been noted to have elevated body fat mass, waist circumference, and body fat percentage relative to non-frail older adults.[27] Frailty is also characterized by underweight status with lower basal metabolic rates and increased inflammation.[27-30]

Table 1. Body Composition and Features of Frailty, Sarcopenia, and Cachexia[23-30]

Features	Sarcopenia	Frailty	Cachexia
Muscle mass	↓	↓	↓
Muscle strength and function	↓	↓	↓
Fat mass	↑	↑	↓, ↔
Basal metabolic rate	↓	↓	↑
Inflammation	↔	↑	↑
Overall body weight	↔	↓	↓

2.1.2. Frailty Prevalence Among Older Adults with Cancer

Advanced age is one of the strongest risk factors for developing cancer, and with half of new US cancer diagnoses occurring among patients age 65 or older, cancer is broadly a disease of aging.[1] Frailty also increases with age and is considered a common geriatric

syndrome. Based on the National Health and Aging Trends Study, 45.5% (95% Confidence Interval, CI, 44.0 to 46.9%) of non-nursing-home US older adults were estimated to be prefrail in 2011; 15.3% (14.2 to 16.4%) were considered frail.[31] The prevalence of frailty is even higher among older adults with cancer. One 2015 systematic review reported a median prevalence of 42% (range 6-86%).[2] Among studies that assessed frailty using comprehensive geriatric assessment (GA, CGA), the prevalence of frailty ranged from 43-64% for cancer studies using ≥2 deficits to define frailty and 22-56% for studies using ≥3 deficits.

2.1.3. Frailty and Adverse Outcomes from Cancer Treatment

Compared to fit cancer patients, frail patients experience more long- and short-term adverse outcomes related to therapy:

Tolerance of treatment side effects—In one US registry study of non-metastatic breast cancer patients (n=660, ≥65 years, 1997-2006), frailty was estimated to increase the odds of patients reporting poor tolerance of treatment side effects when defined as deficits in ≥3 GA domains (odds ratio, OR = 4.86; 95% CI 2.19 to 10.77).[32] Compared to patients with no GA domain deficits, poor treatment tolerance was reported 2-to-4-times more frequently for patients with domain deficits (11% vs. 22%, 34%, 43%, and 44% for patients with 0, 1, 2, 3, or 4 GA domain deficits, respectively).

Post-surgical complications—One multi-center Norwegian study of colorectal cancer patients (n=159, 2006-2008) reported that frail elderly patients (≥70 years) with any pre-operative CGA deficit experienced more 30-day complications and more 30-day complications that were grade II or worse (76% and 62%, respectively, vs. 48% and 33% for fit patients).[33] A separate South Korean study (n=240, mean 76.7 years, 2009-2014) with CGA reported that “high-risk” (≥2 domain deficits) elderly patients undergoing major elective surgery for primary colorectal cancer

had 2-times the odds of major (grade II-V) 30-day post-operative complications (OR = 2.11, 95% CI 1.17 to 3.80).[34]

Chemotoxicity— In a 2019 US multi-site pilot study of patients with newly diagnosed non-small cell lung cancer (n=48, ages 42-86 years), frailty was associated with higher odds of grade 3-5 toxicity during the first two chemotherapy cycles. Elevated odds were estimated when using the Fried Frailty Index (≥3 impairments OR = 7.0, 95% CI 1.1 to 44.6) and GA toxicity risk scores (>7 risk score OR = 4.3; 1.0 to 17.7).[35] In another multi-center study of predominantly gastrointestinal, lung and genitourinary patients in Spain (n=540, mean 68.5 years, 2014-2018), one survey tool used to detect frailty, the Vulnerable Elders Survey 13 (VES-13), was associated with increased odds for grade 3-5 toxicity (VES-13 score >5 OR = 1.54, 95% CI 1.02 to 2.06).[36] Furthermore, in one study of Canadian older adults with cancer (n=100, median 74.1 years, 2007-2008), individual frailty markers were associated with grade 3-5 treatment toxicity at 3 months (low grip strength OR = 4.44, 95% CI 1.03 to 19.20; poor nutritional status OR = 3.60, 1.20 to 10.77).[15]

Because of its association with treatment-related adverse events, identifying frailty has value for determining treatment course and patient safety. Thus, GAs and frailty screening tools are useful for optimizing treatment course completion and patient quality of life.

2.2. Measures to Assess Frailty in Older Adults with Cancer

2.2.1. Geriatric Assessment

The GA is a clinical tool that has been recommended by the International Society of Geriatric Oncology (SIOG) and the American Society of Clinical Oncology (ASCO) for determination of frailty status.[5,37] For older adults receiving chemotherapy, ASCO specifically recommends GA to identify vulnerabilities or geriatric impairments that are not regularly captured in oncology assessments.[5] At a minimum, it is recommended that GA should include assessment of function, comorbidity, falls, depression, cognition, and nutrition. Other health areas that may be assessed are vision, hearing, urinary continence, osteoporosis, polypharmacy, and socioenvironmental circumstances which includes social interaction network, available support resources, special needs, and environmental safety.[38] Many of these domains, such as falls and impairments in activities of daily living (ADLs), have been shown to be modifiable with effective intervention before or during treatment.[39,40] Thus, GA is useful for identifying nononcologic problems and can inform cancer management.

Based on a recently published ASCO task force survey, GA domains are not always assessed by oncologists before starting chemotherapy.[4] While more than half (57.0-69.7%) of surveyed oncologists reported assessing functional status, and nearly half (47.6-57.9%) reported assessing nutritional status, the majority of surveyed oncologists did not assess other GA domains: 27-42% assessed social activity, 25-37% assessed physical performance, 20-32% assessed cognition. Time and resources are cited as barriers to implementing GA into clinical practice as a full outpatient multidisciplinary GA may take up to two hours to complete, not including time for review and management planning.[41] This includes evaluations from physicians, nutritionists, social workers, and physical and occupational therapists.[38] Fortunately, brief comprehensive GAs and geriatric screening tools have been developed and validated for use in oncology patients.[41,42]

The brief, but comprehensive cancer-specific GA developed by Hurria and the Cancer and Aging Research Group (CARG) was designed to be primarily self-administered and mean time to completion was reported to be 27 minutes (range: 8-45 minutes).[41] **Table 2** below presents the measures for the seven domains assessed in the Hurria et al. comprehensive GA.

Table 2. Domains Assessed in the Cancer-Specific Geriatric Assessment Proposed by Hurria *et al*.[41]

Domain	Measures	No. of Items
Functional status	1.) Activities of Daily Living 2.) Instrumental Activities of Daily Living 3.) Karnofsky physician-rated performance rating scale 4.) Karnofsky self-reported performance rating scale 5.) Timed Up and Go 6.) Number of falls in last 6 months	10 7 1 1 1 1
Comorbidity	Physical Health Section	48
Cognition	Blessed Orientation-Memory-Concentration test	6
Psychologic	Hospital Anxiety and Depression Scale	14
Social functioning	MOS Social Activity Limitations Measure	4
Social support	1.) MOS Social Support Survey 2.) Seeman and Berkman Social Ties	13 4
Nutrition	1.) BMI 2.) Percent unintended weight loss in the last 6 months	1 1

BMI = body mass index, MOS = Medical Outcomes Safety.

2.2.2. Geriatric Screening Tools

Multiple geriatric screening tools have been developed for the general older adult and cancer population. **Table 3** presents select geriatric screening tools summarized in a 2018 review.[42] These tools require less than 10 minutes to complete and have items that assess several geriatric domains or consist of selected questions from validated geriatric tools (e.g.,

Geriatric Depression Screen and Mini-Mental Status Exam). Additionally, many GAs use patient-reported information that can be easily completed in the waiting room and do not require additional staff to administer.[43] The University of Alabama at Birmingham (UAB), has recently implemented patient-reported GAs for new patients with gastrointestinal malignancies, and 100% of patients are able to complete the short 6-page questionnaire for GA (Cancer and Aging Resilience Evaluation, CARE, tool, median time = 10 minutes, interquartile range, IQR, 10-15.7 minutes).[6]

Table 3. Selected Geriatric Screening Tools and Reported Validation Measures for Abnormal Comprehensive Geriatric Assessment—Summarized from Loh *et al*. 2018[42]

Tool	No. of items	Time to perform (minutes)	Sensitivity for Abnormal CGA (%)	Specificity for Abnormal CGA (%)	PPV (%)	NPV (%)
Geriatric 8	8	4.4	65-92	3-75	44-86	8-78
Vulnerable Elders Survey-13	13	5.7	39-88	62-100	60-100	18-88
Triage Risk Screening Tool	5	2	91-92	42-50	81-87	63
Abbreviated CGA	15	4	51	97	97	48
Fried frailty criteria	5	5	37-87	49-86	77-95	16-66

CGA = comprehensive geriatric assessment, NPV = negative predictive value, PPV = positive predictive value.

Fried frailty criteria—In longitudinal observational studies, frailty is commonly measured with the five-criteria physical frailty phenotype (PFP) assessment proposed by Fried *et al*. in 2001.[12] The Women's Health and Aging Study (WHAS) and the Atherosclerosis Risk in Communities (ARIC) Study are two such cohort studies that use the Fried criteria.[11,44] **Table 4** presents the criteria used to operationalize the phenotype of frailty. At least 3 deficits are required for classification of

frailty phenotypes, and intermediate or prefrail status is considered for patients with 1 or 2 criteria present.

Table 4. Fried Criteria for Classification of Frailty Phenotype[12]

Characteristics of Frailty	Measure
Shrinking: Unintentional weight loss or sarcopenia	>10 pounds lost unintentionally in prior year
Weakness	Grip strength in the lowest 20% (by gender, BMI)
Poor endurance; exhaustion	Self-reported "exhaustion"
Slowness	Walking time/15 feet in the lowest 20% (by gender, height)
Low activity	Kcals/week in the lowest 20% Males: <383 Kcals/week Females: <270 Kcals/week

BMI = body mass index, Kcals = kilocalories.

CARE Survey—The CARE survey is a modified GA adapted from the GA developed by Arti Hurria and colleagues.[6,45] This survey was developed by Williams *et al*. at UAB, and is performed for all new patients over the age of 60 meeting with the gastrointestinal oncology team at UAB. The fully patient-reported assessment is tailored to a gastrointestinal cancer population and can be completed without involving additional staff. Patients report on 44 items evaluating essential domains of the GA including functional status, physical function, nutrition, health-related quality of life, social support, social activities, psychological status, cognitive function, comorbidities and polypharmacy.

2.2.3. Muscle Measures from Computed Tomography and Myosteatosis

Computed tomography (CT) scans can be used to characterize body composition noninvasively and are frequently used in oncology for cancer staging and monitoring.[46] Axial

images at the third lumbar spine vertebra (L3) are the most common imaging approach for body composition analysis; however, other approaches focused on the psoas muscles or muscles at the fourth thoracic vertebra (T4) cross-section also have prognostic value.[47,48]

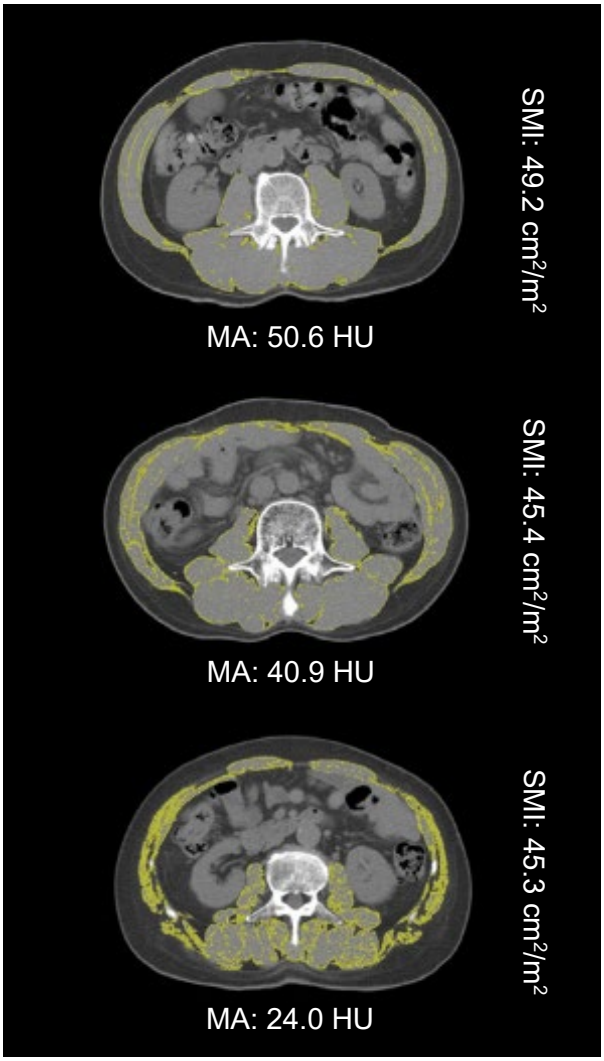
CT measures of skeletal muscle density (SMD) and myosteatosis have been shown to be superior to quantity measures when determining frail status and projecting prognosis.[49] From CT scans, skeletal muscle quantity can be determined using skeletal muscle index (SMI) which is the area of skeletal muscle in the image normalized by the height of the patient (units: cm^2/m^2).[49] SMD is determined using software that identifies low-density muscle tissue in the skeletal muscle area, and measures of SMD (e.g., biopsy or radiological imaging) reflect muscle lipid content.[50,51] SMD is estimated by taking the average density of the skeletal muscle in the cross-sectional image (units: Hounsfield units, HU), and the overall attenuation of the muscle characterizes myosteatosis—the physiological process of fat infiltration into muscle.[51] In aging skeletal muscle, myosteatosis occurs over time, and the increase in intermuscular adipose tissue lowers the muscle density. Myosteatosis and the resultant low-density skeletal muscle have been implicated in incident mobility limitations in well-functioning older adults and are able to account for differences in muscle strength not attributed to muscle quantity.[52,53] In the Health, Aging and Body Composition (Health ABC) study, adjusted 2.5-year risks for incident mobility limitations, defined as self-reported difficulty walking one-quarter mile and climbing 10 steps without resting, for participants in the lowest quartile of mid-thigh muscle density were 1.68- to 1.92-times the risk of participants in the highest quartile of muscle density (HR = 1.92, 95% CI 1.31 to 2.83 for men; HR = 1.68, 1.20 to 2.35 for women).[52]

In cancer registry samples, SMD has shown to be a stronger identifier of frailty status, instrumental activities of daily living (IADL), and walking difficulties compared to measures of muscle quantity (e.g., SMI).[49,54] In the Carolina Senior Registry of older adults with cancer, 5-HU decreases in SMD were shown to be associated with the prevalence of frailty identified through

GA (age- and gender-adjusted prevalence ratio, PR = 1.20, 95% CI 1.09 to 1.32), while decreases in SMI were not associated in unadjusted or adjusted estimations (adjusted PR = 0.95, 0.84 to 1.07).[49] Thus, myosteatosis and SMD have utility in identifying cancer patients who may be frail, and this utility extends to predicting survival. One recent meta-analysis assessing the impact of myosteatosis on overall survival in patients with cancer found that patients with myosteatosis had 75% greater mortality risk compared to non-myosteatosis patients (HR = 1.75, 95% CI 1.60 to 1.92, n = 40 studies).[47] In this summary, myosteatosis was reported to have prognostic value in patients with gynecological, renal, periampullary/pancreatic, hepatocellular, gastroesophageal, and colorectal carcinoma, and lymphomas.

Figure 1 below depicts three patients with similar measures of muscle quantity (SMI between 45 and 49), but different SMDs based on CT images of the L3 vertebra. Yellow shading marks areas of muscle attenuation from -29 to 29 HU, indicating areas of low SMD. Below each image is the mean muscle attenuation value for each patient's cross-section. While having similar quantifies of muscle tissue according to SMI, patient C has a much lower SMD at the L3 cross-section compared to patient A and B. For patients with cancer, these differences in SMD and muscle quality are proposed to contribute to mortality[55]

Figure 1. Cross-Sectional Computed Tomography Images of the L3 vertebra for Quantifying Body Composition Variables—from Fujiwara *et al*. 2015[55]



HU = Hounsfield units, MA = muscle attenuation, SMI = skeletal mass index.

2.2.4. Health Profiles of Older Adults with Cancer Identified from Geriatric Assessment Tools

Previous work has reported on health profiles that could be operationalized from GA items and are listed in the **Table 5** below. Both Balducci and Extermann[56] and the working group of the International Society of Geriatric Oncology (SIOG)[57] incorporated IADLs and ADLs to capture moderately impaired and strongly impaired patients. The SIOG Prostate Cancer Task Force focused on identifying patient groups for older men (≥70 years) with prostate cancer

whereas the Balducci and Extermann and ELCAPA (ELderly CAncer PAtients) study categorizations were devised for older adults with multiple cancer types. To our knowledge, there are no known health profiles operationalized for patients with gastrointestinal cancers for which treatment modalities may differ from other cancer types.

Table 5. Publications Identifying Patient Groups from Geriatric Assessment Items

Reference	Assessment Tools	Identified Patient Groups
Balducci and Extermann 2000[56]	Comprehensive geriatric assessment	(1) Functionally independent on IADLs and ADLs and without serious comorbidity (2) Dependence on at least one IADL and/or presence of one or two comorbid conditions (3) Frail patients
Droz J-P, Balducci L, Bolla M, *et al*. 2010.[57] ISOG working group	(1) CISR-G scale (comorbidities) (2) IADL and ADL (dependence status) (3) 3-month weight loss (nutritional status)	(1) Healthy or fit patients with no serious comorbidity, no functional dependence, and no malnutrition (2) Vulnerable patients with dependence in IADL but no dependence in ADL, or presence of one comorbid uncontrolled condition, or risk of malnutrition (3) Frail patients with ADL impairment, or two or more uncontrolled comorbid conditions, or severe malnutrition (4) 'Too sick' patients with poor health status from a combination of different impairments
Ferrat E, Audureau E, Paillaud E, *et al*. 2016.[58] ELCAPA survey	Indicators selected from geriatric assessment: (1) ADL (functional impairment) (2) MMSE (cognitive impairment) (3) 6- or 1-month weight loss, and/or BMI, and/or MNA score, and/or serum albumin (4) Inadequate social environment (5) Depression criteria on DSM-IV identified from interview (6) Severe (grade 3-4) comorbidities on CISR-G scale	(1) Relatively healthy (2) Malnourished (3) Cognitive and/or mood impaired (4) Globally impaired

ADL = activities of daily living, BMI = body mass index, CISR-G = Cumulative Illness Score Rating-Geriatrics, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, IADL = instrumental activities of daily living, ISOG = International Society of Geriatric Oncology, MMSE = Mini-Mental State Examination, MNA = Mini-Nutritional Assessment.

2.3. Diabetes, Cancer, and Frailty

2.3.1. Diabetes Prevalence Among Older Adults with Cancer

Based on the 2011-2012 National Health and Nutrition Examination Survey (NHANES), the overall prevalence of diagnosed and undiagnosed diabetes in the US adult population is estimated to be 14.3% (95% CI 12.2 to 16.8%).[59] However, the burden of diabetes increases with age; diabetes was estimated to be prevalent in 17.4% (14.4 to 21.0%) of middle-aged adults (45-64 years) and 33.0% (27.1 to 39.4%) of older adults. The same trend can be seen with prediabetes; 28.2% (24.4 to 32.4%) of young adults (20-44 years) have prediabetes relative to 44.9% (37.6 to 52.4%) and 49.5% (43.4 to 55.6%) of middle-aged and older adults, respectively.

Among US older adults with cancer, diabetes is also common. One recent study reported the prevalence of comorbid diabetes among US older adults with cancer using data from the National Cancer Data Base (NCDB) and the linked data of the Surveillance, Epidemiology, and End Results (SEER) Program and Medicare claims up to 2010. For colorectal cancer, diabetes prevalence ranged from 14.8% to 25.9% depending on the data source and whether disease was defined using a look-back period for claims.[60] For breast cancer and non-small cell lung cancer—two other commonly diagnosed cancers in the US—the prevalence of comorbid diabetes ranged from 10.8% to 20.7% and from 12.5% to 23.1%, respectively. Therefore, for these cancers, up to one quarter of older adult patients may have comorbid diabetes which could have implications for frailty, treatment tolerance, and treatment adverse events.

2.3.2. Older Adults with Cancer and Diabetes—A Potentially Vulnerable Population with Complex Care Needs

Frail individuals and those with chronic conditions are underrepresented (or excluded) from trials. Among US phase III or phase IV studies recruiting older adults, study inclusion is

often limited based on the Eastern Cooperative Oncology Group (ECOG) performance status.[61] Recruitment is commonly restricted to patients with ECOG grades of 0-1, and some include patients grades of 0-2. **Table 6** presents the grades for the ECOG criteria. Patients with scores of 2, 3, and beyond begin to have limitations with work capabilities, walking, and self-care. In terms of chronic diseases, some chemotherapy phase III/IV studies exclude patients based on cardiovascular or renal disease, uncontrolled medical conditions (e.g., hypertension), or co-morbid diseases that may be suspected to impact treatment tolerance or safety assessments. For these chemotherapy studies, eligibility criteria often exclude patients with prior sensory or motor neuropathy from any cause. Because diabetes is associated with neuropathy, this criterion likely excludes patients with diabetes from essential safety studies. Thus, study recruitment is often limited to fit patients who are unlikely to be frail or have debilitating chronic disease.

Table 6. Eastern Cooperative Oncology Group (ECOG) Criteria for Performance Status

Grade	Criteria
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Because of the lack of evidence from trials, treatment decision-making is challenging in frail older adults and those with comorbid conditions like diabetes. Current treatment dosing

guidelines for chemotherapy do not consider comorbidities and are based primarily on body surface area (BSA). This dosing approach was originally derived in 1916; and despite only incorporating height and weight measurements, BSA has been a common method to achieve dosing uniformity in cytotoxic trials since the 1960s.[62] BSA is even recommended for dosing patients with obesity.[63,64] However, there is evidence that this dosing approach is invalid for optimizing and individualizing doses, and its use has been associated with highly variable drug plasma levels and patient pharmacokinetics.[62,65-69] Variabilities in drug level and clearance greatly impact the occurrence of toxicity and treatment failure.[66] Therefore, strategies beyond BSA that consider comorbidities, aging and effects on body composition are needed to prevent treatment complications. Further, because diabetes and myosteatosis are plausibly linked, older adults with cancer and diabetes may represent a patient population with low muscle quality and thus may be particularly vulnerable to treatment complications. Thus, there is a need to generate evidence on the link between diabetes and frailty in patients with cancer and to understand how these intersecting concepts influence treatment delivery and outcomes in clinical practice.

2.3.3. Evidence Linking Frailty and Diabetes

The occurrence of both diabetes and frailty increases with age, and there is evidence that diabetic individuals are more likely to be frail. In cross-sectional estimates, one 2014 editorial in the Journal of the American Medical Directors Association cites a range of frailty prevalence from 32-48% for older adults with diabetes—much higher than the 5-10% cited for the general population.[70]

Based on longitudinal studies, diabetes may be associated with the onset of frailty. Strong evidence for this association comes from an analysis of women ages 70 to 79 in The Women's Health and Aging Study II using glycosylated hemoglobin A1c (HbA1c) testing.[71] HbA1c levels are a measure of average blood sugar levels over the past 2-3 months with higher

percentages indicating poor blood sugar control and hyperglycemia. Compared to women in the lowest HbA1c group (<5.5%) at baseline, women with HbA1c levels ≥8.0% had more than 3-times the risk of developing frailty when using the criteria for frailty phenotype (mean follow-up 8.6 ± 3.6 years; adjusted HR = 3.33, 95% CI 1.24 to 8.93)[12,13,71] Differences for the other HbA1c levels when compared to the lowest group were as follows: 6.5-7.9% HR = 1.04, 0.40 to 2.70; 6.0-6.4% HR = 1.25, 0.58 to 2.69; 5.5-5.9% HR = 1.29, 0.65 to 2.55. Risks were also greater for developing difficulties with walking (HR = 3.47, 1.26 to 9.55), low walking speed (HR = 2.82, 1.19 to 6.71), and low physical performance as measured by the Short Performance Physical Battery (HR = 3.60, 1.52 to 8.53). Other longitudinal studies link diabetes to physical deficits that could be associated with frailty such as muscle strength, function, and disability. These are summarized in **Table 7**. With regards to the role of obesity, three studies note that BMI or body fat percentage are associated with the development of frailty and functional limitations independent of diabetes status[71-73]. Among women with diabetes, one study reported that BMI was a predictor of any disability (HR = 2.00, 1.39 to 2.89 for BMI ≥30 vs. <25; HR = 1.40, 0.97 to 2.01 for BMI 25-29.9 vs. <25).[74]

Table 7. Studies Assessing the Longitudinal Association Between Diabetes and Hyperglycemia with Losses in Muscle Strength, Function, and Disability

Outcome	Population	Results
DIABETES		
Strength	Health ABC Study—Park 2007[75] N=1,840 (70-79 years) n=305 with type 2 diabetes	3-year changes in knee extensor strength (maximal torque, Newton-meters, Nm): • Diabetes vs. no diabetes = -15.7 ± 1.1 Nm vs. -12.5 ± 0.5 Nm (when adjusting for demographics, BMI, baseline strength/quality, changes in leg lean mass, physical activity, and clinical conditions) 3-year changes in knee extensor muscle quality (specific torque, Nm/kg): • Diabetes vs. no diabetes = -1.64 ± 0.14 Nm/kg vs. -1.21 ± 0.06 Nm/kg No differences in 3-year changes in hand grip strength or quality between diabetes vs. no diabetes
Walking speed/function	Study of Osteoporotic Fractures—Lee 2013[76] N=2,864 women (mean 78.5 years) n=185 with diabetes, n=28 with diabetes and insulin sensitizer;	Over 4.9 years: • Women with diabetes had greater losses in usual walk speed vs. no diabetes (-0.16, 95% CI -0.19 to -0.14 vs. -0.11, -0.12 to -0.11) • Women with diabetes had greater losses in rapid walking speed (-0.21, -0.24 to -0.17 vs. -0.15, -0.16 to -0.14) • No difference in changes in grip strength (-1.44, -1.90 to -0.98 vs. -1.26, -1.38 to -1.14) Women with diabetes taking insulin sensitizers had fewer losses in rapid walking speed vs. women with diabetes (-0.10, -0.16 to -0.03 vs. -0.17, -0.20 to -0.15)

Disability	Women's Health and Aging Study—Volpato 2003[77]
	
	Cohort eligibility included difficulty performing functional tasks
	
	N=729 (mean 77.4 years)
	n=105 with diabetes
		3-year adjusted RR for disability (diabetes vs. no diabetes):
		• Mobility disability RR = 1.63 (95% CI 1.12 to 2.36)
		• ADL disability
		  • Overall RR = 1.39 (0.99 to 1.94)
		  • Among women with 19-36 months follow-up, RR = 2.18 (1.33 to 3.60)
		  • Among women with 1-18 months follow-up, RR = 0.91 (0.56 to 1.48)

Functional disability	Study of Osteoporotic Fractures—Gregg 2002[74] N=8,344 women (mean 71.3 years) n=527 with diabetes	Onset of disability (inability to perform physical/household tasks), median (max) follow-up = 8.8 (12.3) years: • Adjusted HR for diabetes vs. no diabetes = 1.42 (95% CI 1.23 to 1.65)

Functional disability	Sacramento Area Latino Study on Aging (SALSA)—Wu 2003[72]
	
	N=1,789 (mean 70.6 years)
	n=585 with diabetes
		From baseline (1998-1999) until visit 2 (2001):
		• Diabetes was associated with changes in activities of daily living (GEE regression estimate 0.031, 95% CI 0.004 to 0.058)
		• Diabetes was associated with changes in instrumental activities of daily living (0.062, 0.033 to 0.092)
		• Diabetic subjects with longer diabetes duration had greater odds to report IADL limitations vs. those with shorter diabetes duration
		  • 11-20 vs. ≤10 years OR = 1.03 (0.98 to 1.07)
		  • 21-30 vs. ≤10 years OR = 1.08 (1.01 to 1.15)
		  • >30 vs. ≤10 years OR = 1.10 (1.02 to 1.18)

HYPERGLYCEMIA		
Grip strength	Rancho Bernardo Study—Kalyani 2015[78] N=636 (mean 71.3 years) Mean follow-up = 7.4 ± 5.7 years	In fully adjusted models: • Higher fasting plasma glucose was associated with greater estimated losses in hand grip strength for men: -0.44 ± 0.22 per 1 SD increase in fasting plasma glucose • Higher 2-hour glucose levels were associated with greater estimated losses in hand grip strength for men: -0.39 ± 0.25 per 1 SD increase in 2-hour glucose levels • Fasting plasma glucose had weak estimated associations with grip strength for women: -0.02 ± 0.12 per 1 SD increase in fasting plasma glucose • Higher 2-hour glucose levels were associated with greater estimated losses in hand grip strength for women: -0.20 ± 0.14 per 1 SD increase in 2-hour glucose levels
Fitness test	Helsinki Birth Cohort Study—Astrom 2018[73] N=1,078 (mean 61.3 years)	In fully adjusted models, patients with impaired glucose tolerance, newly diagnosed diabetes participants, or previously known diabetes had lower estimated performance on Senior Fitness test at 10 years (vs. normoglycemic participants):

	Mean follow-up time = 9.7 ± 0.9 years	• Impaired glucose tolerance *b* coefficient = -2.56 (-4.96 to -0.16) • Newly diagnosed diabetes *b* = -5.49 (-9.26 to -1.72) • Previously known diabetes *b* = -11.56 (-16.15 to -6.98) When assessing Senior Fitness test components, participants with impaired fasting glucose, newly diagnosed diabetes, or previously known diabetes had consistently lower estimated performance across all components(vs. normoglycemic participants): • Chair stand *b* coefficient range = -0.29 to -1.95 across groups vs. normoglycemic participants • Arm curl *b* range = 0.71 to -2.25 • Back scratch *b* range = -0.36 to -2.85 • Chair sit-and-reach *b* range = -0.51 to -1.14 • 6-min walk *b* range = -0.50 to -3.38
HbA1c		
Frailty, Walking ability, fitness test	Women's Health and Aging Study II—Kalyani 2012[71] N=329 (mean 73.9 years) Mean follow-up of 8.6 ± 3.6 years	≥8.0% HbA1c vs. <5.5% • Incident frailty HR = 3.33 (1.24 to 8.93) • Incident walking difficulty HR = 3.47 (1.26 to 9.55) • Incident low walking speed HR = 2.82 (1.19 to 6.71) • Incident low physical performance HR = 3.60 (1.52 to 8.53)
Muscle strength	Baltimore Longitudinal Study of Aging—Kalyani 2015[79] N=984 (mean 58.8-68.3 years) Mean follow-up ~1.9 ± 2.2 years (range 0-7.5 years)	≥6.1% HbA1c vs. <5.5% • Knee extensor strength -4.47 ± 2.32 Nm

BMI = body mass index, FPG = fasting plasma glucose, GEE = generalized estimating equation, hbA1c = hemoglobin A1c, HR = hazard ratio, IADL = instrumental activities of daily living, Nm = Newton-meters, RR = risk ratio.

Three longitudinal studies also document an association between diabetes and skeletal muscle loss. In the Health ABC cohort, undiagnosed or diagnosed diabetes was associated with greater losses in either total, trunk, or appendicular lean mass.[80] Women in the cohort with diabetes were additionally noted to have greater losses in thigh cross-sectional area. Other cohort studies provide evidence for these excessive lean mass losses with mixed consensus on how diabetes and insulin resistance impact changes in fat mass, particularly trunk fat.[80-82] In treatment studies, multiple reports document improvements in lean mass and losses of fat mass within 6 months of initiating antidiabetic treatments.[83,84] Thus, diabetes status appears to at least be associated with changes in skeletal muscle composition which has implications for the onset of frailty and other functional deficits.

While diabetes, hyperglycemia, and insulin resistance are associated with changes in muscle mass, diabetes has been shown to be associated with one aspect of muscle composition that has recently gained attention for its association with frailty—skeletal muscle quality as characterized by SMD.[49] This muscle metric identifies myotsteatosis, and diabetes is one co-morbidity that has been shown to be associated with myosteatosis in cross-sectional and longitudinal studies.[17,85-92] Human studies have documented the cross-sectional association of myosteatosis and insulin resistance using muscle biopsies of nondiabetic patients, nuclear magnetic resonance spectroscopy, and imaging.[85-88] Among studies using CT or magnetic resonance imaging (MRI), the cross-sectional association has been noted when using attenuation coefficients to measure muscle density and when quantifying the adipose tissue content within specific muscle compartments.[86,88-91] Differences in SMD have also been proposed to partially explain ethnic differences in insulin resistance prevalence.[92] Among longitudinal assessments of the diabetes-myosteatosis association, the only known study comes from the Health ABC Study where older men (70-79 years at baseline) with diabetes were shown to experience greater 5-year increases in thigh intermuscular fat compared to men without diabetes (56.5 ± 5.4% vs. 44.6 ± 3.2% for men with diabetes vs. without).[17] Notably, no

differences were reported for women (31.4 ± 4.3% vs. 28.7 ± 2.1% for women with diabetes vs. without) which may have implications for how SMD identifies frailty in this population. Several cancer studies have also documented the diabetes-myosteatosis association cross-sectionally and are summarized in **Table 8** below.[55,93-96]

Table 8. Cancer Studies Providing Cross-sectional Evidence for the Association between Diabetes and Myosteatosis

Study	Cancer Population	Results
Xiao 2018[97]	Patients with non-metastatic colorectal cancer N=3,051 (mean 63.2 years)	Patients with diabetes without complications were more prevalent in the normal-SMI-low-SMD group relative to the normal-SMI-normal-SMD group (PR = 1.45, 95% CI 1.04 to 2.02) Patients with diabetes with complications were more prevalent in the normal-SMI-low-SMD group relative to the normal-SMI-normal-SMD group (PR = 1.90, 1.24 to 2.92)
Van Rijssen 2017[94]	Patients undergoing pancreatoduodenectomy N = 166, excluding pancreatic ductal adenocarcinoma (mean 64.8 years)	Patients with normal MA index values had a lower prevalence of diabetes compared to patients with low MA index values (9.4 vs. 21.0%) No difference in diabetes prevalence when comparing patients based on normal vs. low SMI (13.9 vs. 15.4%)
Kaibori 2015[93]	Patients undergoing heptaocellcular carcinoma resection N = 141 (53-55% ≥69 years)	Patients with low IMAC had a lower burden of diabetes compared to patients with high IMAC (14 vs. 30%) HbA1c % for patients with low IMAC = 5.68 ± 0.82 HbA1c % for patients with high IMAC = 6.00 ± 1.14
Fujiwara 2015[55]	Patients diagnosed with hepatocellular carcinoma N=1,257 (mean 68.8 years)	Patients with low MA had a greater prevalence of diabetes (27.4 vs. 23.4%)
Stretch 2018[98]	Patients undergoing pancreaticoduodenectomy for pancreatic or non-pancreatic periampullary adenocarcinoma N=123 (mean 73.5 years for <30 HU patients, 63.3 years for ≥30 HU patients)	Patients with low muscle radiodensity (<30 HU) had a greater prevalence of diabetes (41.9% for <30 HU patients vs. 16.3% for ≥30 HU patients)

HU = Hounsfield units, IMAC = intramuscular adipose tissue content, MA = muscle attenuation, PR = prevalence ratio, SMD = skeletal muscle density, SMI = skeletal muscle index.

Patients with diabetes may therefore have a higher burden of myosteatosis, or they may experience more myosteatosis and greater losses in SMD over time. The resultant poor muscle quality may confer susceptibility for developing functional, strength, and nutritional deficits that may be captured in frailty domains. In patients with cancer, this diabetes-myosteatosis association may impact the performance of SMD in identifying frailty, and more research into conditions that affect myosteatosis may be needed given recent findings linking chemotherapy drug metabolism with lean body mass and total adipose tissue.[99]

2.3.4. Proposed Biological Mechanisms for the Diabetes-Myosteatosis Association

Intramyocellular fat accumulation (fat within muscle cells)—In human studies, increased fat accumulation in muscle and liver tissue have been reported to be associated with the insulin resistance seen in elderly patients.[87] This resistance is attributable to reduced insulin-stimulated muscle glucose metabolism.[87,100] It is hypothesized that increased fatty acid concentrations in skeletal muscle either 1.) decreases muscle glucose uptake by inhibiting an enzyme that would normally allow glucose to enter glycolysis and be broken down; the result is a buildup of glucose in the cell and thus reduced glucose uptake from blood; or 2.) increases fatty acid metabolites which leads to the phosphorylation of insulin receptor substrates and reduced insulin receptor signaling and glucose transport activity.[101] In both proposed mechanisms, mitochondrial dysfunction results in low uptake of glucose from the blood and subsequent insulin resistance. It should be noted that the reverse has also been hypothesized whereby the mitochondrial dysfunction seen in diabetes and aging may actually lead to increased intramyocellular fat accumulation.[102] Therefore, it is not fully clear whether intramyocellular fat accumulation is a marker or cause of insulin resistance, and there may be some feedback mechanism between the two.[51] Furthermore, because insulin sensitivity is likely required for optimal muscle protein synthesis after meals, insulin resistance and consequent impaired protein synthesis are

proposed contributors to muscle wasting in cancer and are likely to impact muscle composition.[103,104]

Intermuscular fat (fat cells between muscle tissue)—One theory suggests that intermuscular adipocytes differ from adipocytes from other anatomical sites.[51,105] Local secretion of adipokines from fat cells could induce changes in muscle metabolism and insulin sensitivity. One alternative theory suggests that intermuscular fat may inhibit the effects of systemic insulin on local vasodilation resulting in inhibition of post-meal increases in nutritive blood flow and insulin action[51,106]

2.4. Research Innovation

Several gaps in knowledge remain:

- Imaging metrics that characterize muscle quality (e.g., SMD) have been shown to be associated with frailty; however, screening performance in classifying frailty has not been evaluated in patients overall nor for gender-diabetes subgroups.

- Health and impairment profiles in patients with gastrointestinal cancer remain unexplored.

This study proposes to address these gaps by:

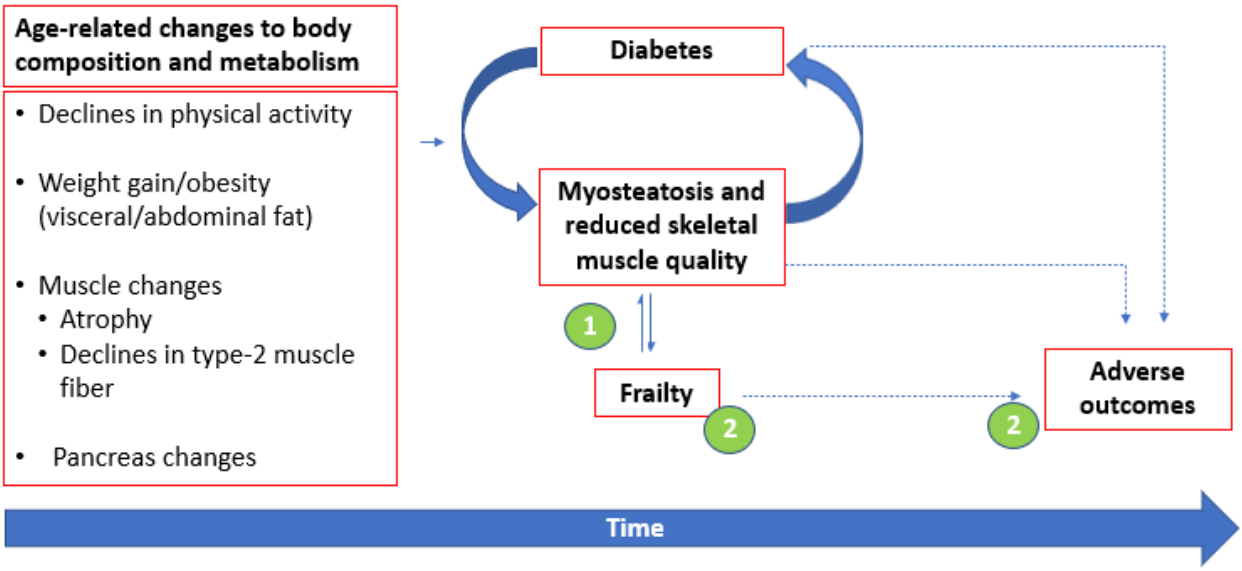
- Using epidemiological methodologies to evaluate the performance of SMD in screening for frailty in patients with and without diabetes and for each gender.

- Using a patient registry with captured geriatric assessment domains to identify and describe impairment profiles in patients with gastrointestinal cancer.

CHAPTER 3. MATERIALS AND METHODS

This research aims to expand our understanding of frailty screening using skeletal muscle metrics and impairment patterns that contribute to frailty in older adults with cancer. **Figure 2** presents a conceptual diagram relating exposures and outcomes for this research. Due to changes in body composition and metabolism that occur with aging, older adults are more predisposed to insulin resistance and diabetes compared to younger adults. This insulin resistance may be associated with underlying muscle quality either as a cause, an outcome, or through some feedback mechanism. Aim 1 will focus on the cross-sectional association between myosteatosis and SMD with GA-identified frailty. It evaluates the screening performance of SMD in classifying frailty in patients with and without diabetes and for each gender. Aims 2 will identify and describe impairment patterns that contribute to pre-frailty and frailty in older adults with GI cancer and describe their association with mortality.

Figure 2. Conceptual Diagram of Biological Pathways Relating Diabetes, Muscle Density, and Frailty, and the Proposed Aims of this Dissertation Research



3.1. Data Source

For the two aims, I propose to use the Cancer & Aging Resilience Evaluation (CARE) Registry—an ongoing single-site registry of older adult patients with cancer at UAB. The overarching goal of the registry is to evaluate implementation of the GA in the routine care of older adult cancer patients referred for initial consultation.[6] GA is a multidisciplinary diagnostic process aimed at determining an elderly person's medical, psychosocial, and functional capabilities and limitations.[107] The registry specifically evaluates the use of the CARE tool—an 82-item, patient-reported version of the GA that captures information on the following domains: physical function, nutrition, cognition, psychological function, social support, comorbidity, and health-related quality of life (HRQOL).[6] Patients are predominantly late-stage and diagnosed with gastrointestinal cancers. Registry recruitment began in fall 2017, and as of February 2022, there have been over 1,526 older adult patients (≥60 years) who have consented to registry evaluations. The overall prevalence of diabetes in the registry is 28%.

3.2. Study Population

Aim 1 is a cross-sectional study of CARE registry patients using baseline CARE tool and imaging assessments. All patients who consented to join the registry are eligible for this study. As of February 2022, nearly 48% (732/1526) of these patients are new GI cancer patients at UAB who reported no chemotherapy history or at least six months of no treatment at baseline. **Table 9** below describes characteristics of patients enrolled in the registry. Aim 2 uses impairment data collected in the CARE tool at registry enrollment and describes the association of latent impairment classes with mortality. Aim 2 specifically focuses on the registry sample with gastrointestinal cancers.

Table 9. Patient Characteristics of the Cancer & Aging Resilience Evaluation (CARE) Registry (University of Alabama at Birmingham, 2017-2022)

Total Patients	**N = 1526**
Age, median (IQR)	68 (64-74)
Sex, n (%)	
Female	615 (40.3)
Male	911 (59.7)
Race	
White	1,137 (74.5)
Black	351 (23.0)
Asian	16 (1.1)
Other	21 (1.4)
Educational level, n (%)	
Less than high school	175 (11.5)
High school graduate	659 (43.2)
Associate/Bachelors	342 (22.4)
Advanced degree	145 (9.5)
Missing	205 (13.4)
Marital status, n (%)	
Single	86 (5.6)
Widowed/divorced	416 (27.3)
Married	818 (53.6)
Unknown	206 (13.5)
Cancer type, n (%)	
Colon	255 (16.7)
Pancreatic	255 (16.7)
Rectal	130 (8.5)
Hepatocellular	106 (7.0)
Neuroendocrine	71 (4.7)
Cholangiocarcinoma	66 (4.3)
Esophageal	50 (3.3)
Gastric	39 (2.6)
Gastrointestinal stromal tumor (GIST)	33 (2.2)
Anal	29 (1.9)
Appendiceal	11 (0.7)
Head and neck	101 (6.6)
Lung	98 (6.4)
Prostate	67 (4.4)
Other	215 (14.1)
Cancer stage, n (%)	
I/II	350 (22.9)
III/IV	1,041 (68.2)
Cancer stage 0 / Missing / Pending	135 (8.9)

IQR = interquartile range.

3.3. Exposure Assessment

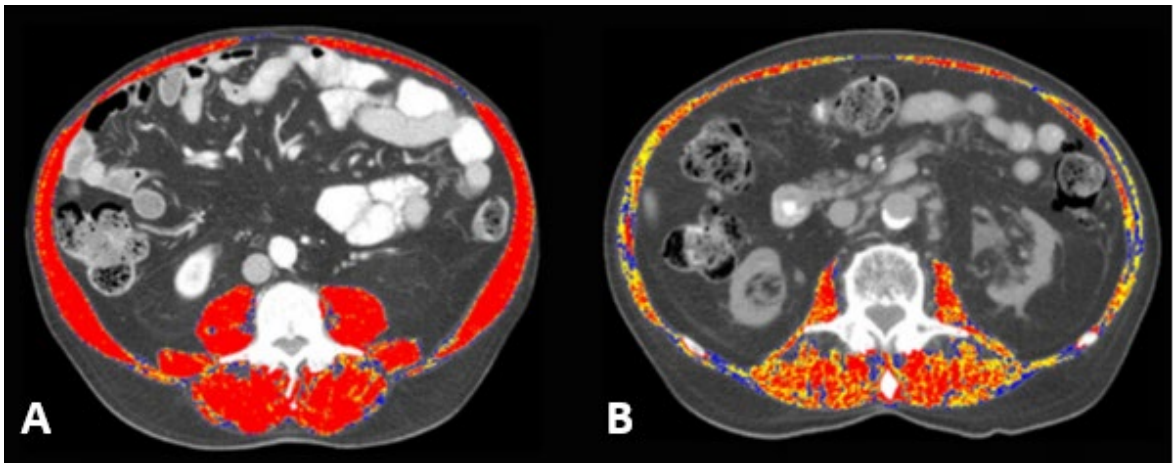
Exposures were assessed using the baseline CARE tool and CT imaging taken within ±60 days of CARE tool completion. Additional demographic information (age and gender) along with clinical characteristics (height, weight, cancer type and stage, current chemotherapy line, and chemotherapy treatment phase) were extracted from electronic health records.

Diabetes status was assessed using the baseline CARE tool. Patients were asked if they have diabetes at the present time (yes/no), and if the illness interferes with their activities (a great deal/somewhat/not at all). The registry has future plans to link patient records for the identification of medications.

Skeletal muscle composition was assessed using a pre-treatment CT imaging cross-section at the L3 vertebra. Each scan was analyzed with automatic tissue segmentation using a proprietary algorithm (https://www.voronoihealthanalytics.com), and the software calculated muscle metrics based on image pixels.[108] This non-invasive method for assessing muscle composition has been shown to be valid compared to the assessment of muscle biopsies.[109] The specific imaging metric of interest was SMD which characterizes myosteatosis. **Figure 3** displays example L3 CT images from two patients with similar body mass index (BMI) but different muscle density. Patient A's skeletal muscle area was composed of more normal density tissue with radiodensity ranging from +30 to +150 HU (red area). Patient's B's skeletal muscle area was composed of lower density tissue as indicated by the yellow (HU range +1 to +29) and blue (HU range 0 to -29 HU) areas. The present study used the continuous form of SMD and gender-specific quartile cut-off points for primary analyses. In secondary analyses, I assessed cut-off points from published cancer studies identified in a 2020 meta-analysis.[47] I specifically explored the BMI-based cut-off points published in Martin *et al*. 2013 which were used to predict survival, and the age- and sex-specific cut-off points from Martin *et al*. 2018 which were defined to predict hospital length of stay (see **Table 10**).[110,111] These criteria were selected because they determined cut-off points using optimal cut-off methods that categorize

based on longitudinal outcomes; these are more clinically meaningfully than distribution-based (e.g., tertile, mean) cut-off points. Additionally, these two studies included patients with metastatic disease, which is relevant given the CARE registry patient population (48% stage IV, 27% stage III among patients with known cancer stage).

Figure 3. Examples of Abdominal Computerized Tomography Images—from Williams *et al*. 2018[49]*



*red = skeletal muscle within the normal range of radiodensity (+30 to +150 Hounsfield Units, HU); yellow = skeletal muscle with radiodensity between +1 to +29 HU; blue = skeletal muscle with radiodensity between 0 to -29 HU.

Table 10. SMD Cut-off Points Identified in a Recent Meta-analysis—Aleixo *et al*. 2020[47]*

Reference	Population	Definition of Low SMD based on Muscle Attenuation (MA)
Cut-off points by BMI		
Martin 2013[110]	Lung or GI cancer Mean age: Men = 64.7 ± 11.2 years Women = 64.8 ± 11.5 years Tumor stage: I (5%), II (16%), III (28%), IV (52%)	BMI < 25: MA < 41 HU BMI ≥ 25: MA < 33 HU
Cut-off points by Sex and Age		
Martin 2018[111]	Colorectal cancer Mean age = 66.6 ± 11.9 years Cancer stage: I = 18%, II = 34%, III = 42%, IV = 5%	Men, Age <50: < 42.0 HU Men, Age 50-59: < 37.6 HU Men, Age 60-69: < 32.9 HU Men, Age 70-79: < 29.7 HU Men, Age ≥80: < 28.1 HU Women, Age <50: < 39.6 HU Women, Age 50-59: < 36.0 HU Women, Age 60-69: < 31.4 HU Women, Age 70-79: < 27.8 HU Women, Age ≥80: < 24.8 HU

BMI = body mass index, CT = computed tomography, GI = Gastrointestinal, Hounsfield Units (HU), L3 = third lumbar, SMD = skeletal muscle density.

*Based on studies of colorectal or gastric cancer patients with CT scanning at the L3 vertebra cross-section.

Geriatric impairments were self-reported in the CARE tool and were dichotomized for use as class indicators in LCA (**Table 11**). This modified GA was adapted from the CARG GA developed by Hurria and colleagues and was tailored to survey a gastrointestinal cancer population using a completely patient-reported assessment.[6,45] Patients reported on all essential domains of the GA including functional status, physical function, nutrition, health-related quality of life, social support, social activities, psychological status, cognitive function, comorbidities and polypharmacy.

Table 11. Impairments Defined in the CARE Registry

Impairment domain	Description	Coding and Missing Responses
Recent falls (1 item)	History of ≥1 falls in the past 6 months: "How many times have you fallen in the last 6 months?"	Impaired: ≥1 fall reported No impairment: 0 falls reported or no response
Walking (1 item)	Significant limitations in walking one block: "Does your health limit you in walking one block?"	Impaired: "limited a lot" No impairment: "not limited at all" or "limited a little"
IADLs (6 items)	Presence of ≥2 limitations in IADLs. "Can you…": • "…get to places out of walking distance" • "…go shopping for groceries or clothes (assuming you have transport) • "…prepare your own meals" • "…do your housework" • "…take your own medicines" • "…handle your own money"	Impaired: ≥2 IADL impairments No impairment: patients with impairments sum <2 and no missing responses on all 6 items
ADLs (3 items)	Presence of any impairment in ADLs. "Can you…": • "… get in and out of bed" • "dress and undress yourself" • "take a bath or shower"	Impaired: ≥1 ADL impairment No impairment: = no limitations and no missing responses on all 3 items
Weight loss (3 items)	Presence of significant weight loss based on patient-reported weight: • "I currently weigh ___ pounds" • "One month ago I weighed about ___ pounds" • "6 months ago I weighed about ___ pounds"	Significant weight loss: ≥3% weight loss within 1 month or ≥6% weight loss within 6 months No significant weight loss: <3% weight loss within 1 month or <6% weight loss in 6 months (only 1 criterion required to report no significant weight loss)
ECOG-PS (1 item)	Limited self-reported activity: "Over the past month, I would generally rate my activity as:"	Impaired: ECOG-PS ≥3 (i.e., able to do little activity and spend most of the day in bed/chair; or pretty much bedridden, rarely out of bed) No impairment: ECOG-PS 0-2 (i.e., normal activity; not feeling up to most things but in bed or chair less than half the day)

		and no missing responses on all 3 items
Social activity interference (1 item)	Interference in social activity: "During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (e.g., visiting friends, relatives)?"	Impaired: Patients responding "most of the time" or "all of the time" No impairment: Patients responding "some of the time", "a little of the time", or "none of the time"
Multimorbidity (13 items)	Presence of ≥4 comorbidities reported on the OARS comorbidity measure: "Do you have any of the following illnesses at the present time?" • Other cancers or leukemia • Arthritis or rheumatism • Glaucoma • Emphysema or chronic bronchitis • High blood pressure • Heart disease • Circulation trouble in arms or legs • Diabetes • Stomach or intestinal disorders • Osteoporosis • Chronic liver or kidney disease • Stroke • Depression	Impaired: ≥4 comorbidities No impairment: 0-4 reported comorbidities (missing response = no comorbidity)
Social support (4 items)	Significant impairment in any tangible support on the MOS-SSS: "Do you have someone to…" • "…help if you were confined to bed?" • "…take you to the doctor if needed?" • "…prepare your meals if you are unable to do it yourself?" • "…help with daily chores if you were sick?"	Impaired: Patients responding "none of the time", "a little of the time" or "some of the time" to any item No impairment: Patients responding "most of the time" or "all of the time" for all 4 items
Anxiety (4 items)	PROMIS Anxiety short form. "In the past 7 days…": • "…I felt fearful" • "…I found it hard to focus on anything other than my anxiety • "…my worries overwhelmed me" • "…I felt uneasy"	Impaired: PROMIS Anxiety T-score >60 and no missing responses No impairment: PROMIS Anxiety T-score ≤60 and no missing responses

Depression (4 items)	PROMIS Depression short form. "In the past 7 days…": • "…I felt worthless" • "…I felt helpless" • "…I felt depressed" • "…I felt hopeless"	Impaired: PROMIS Depression T-score >60 and no missing responses No impairment: PROMIS Depression T-score ≤60 and no missing responses
Cognitive impairment (4 items)	PROMIS Cognitive Function short form. "In the past 7 days…": • "…my thinking has been slow" • "…it has seemed like my brain was not working as usual" • "…I have had to work harder than usual to keep track of what I was doing" • "…I have had trouble shifting back and forth between different activities that require thinking"	Impaired: PROMIS Cognitive Function T-score <40 and no missing responses No impairment: PROMIS Cognitive Function T-score ≥40 and no missing responses
Polypharmacy	Patient reporting ≥9 daily medications: "How many medications do you take on a daily basis?"	Impaired: ≥9 daily medications No impairment: 0-8 daily medications reported and no missing response

ADLs = activities of daily living, IADLs = instrumental activities of daily living, ECOG-PS = Eastern Cooperative Oncology Group Performance Status, MOSS = Medical Outcomes Study Social Support Survey, OARS = Older Americans and Services, PROMIS = Patient-Reported Outcomes Measurement Information System.

3.4. Outcome Assessment

Frailty (Aim 1) was assessed using the CARE tool. Frailty was defined based on the principles of deficit accumulation using 44 health deficit items in the CARE tool; responses were coded as indicating the presence of deficit ('1'), absence of the deficit ('0'), or intermediate responses (e.g., 'sometimes' or 'maybe'; '0.5').[7-9] Based on 44 GA variables from the CARE tool, individuals were assigned scores representing the overall proportion of deficits (range 0-1). Scores of '0' indicated no deficits present; '1' indicated all 44 deficits were present. Prior work has shown that an index constructed of at least 30 variables sufficiently predicts adverse outcomes among older adults.[112,113] In the CARE registry, frailty scores were only calculated for

patients who responded to ≥24 of the 44 health deficit items.[112-114] Scores were categorized using previously defined thresholds for frailty indices to identify patients who were considered robust (0-0.2), pre-frail (0.2-0.35) or frail (>0.35).[115]

Mortality was assessed in Aim 2. Vital status and date of death were identified up to October 2021 using linkage with LexisNexis® and patient name and social security number. Zip code and date of diagnosis were used for confirmation. We reported deaths that occurred up to one year after CARE tool completion.

3.5. Patient Characteristics

Patient characteristics were assessed at baseline as part of the CARE tool and additional information was extracted from electronic health records. **Table 12** summarizes covariates and characteristics. For Aim 2, we additionally categorized cancer type based on high-risk malignancies (pancreatic, hepatobiliary, and esophageal cancers), and low-risk malignancies (colorectal, gastrointestinal stromal tumors [GIST], neuroendocrine tumors, and other) based on typical estimated survival and 1-year mortality.[116]

Table 12. Covariates and Study Sample Characteristics

Covariates and Sample Characteristics	Description
Demographics	Age, gender (male, female), race (White/Caucasian, Black/African American, Native American or Alaskan, Asian, Native Hawaiian, other), ethnicity (Hispanic or Latino, non-Hispanic), education level (less than high school, high school graduate, associate/Bachelors, advanced degree), marital status (single, widowed/divorced, married)
Treatment	Prior chemotherapy (yes, no), treatment, treatment phase (pre-treatment, during, post-treatment)
Cancer	Type (colon, pancreatic, rectal, esophageal, gastric, neuroendocrine, head and neck, lung, prostate, and others), stage (I, II, III, IV)
BMI	BMI (continuous and categories: underweight, normal weight, overweight, obesity)

BMI = body weight index.

3.6. Analytic Methods

Aim 1—Crude associations between SMD and frailty score

We assessed how continuous SMD was continuous frailty score using scatterplots and unadjusted linear regression with R2 values to compare model fit.

Aim 1—Diagnostic Models

Diagnostic models are common in biomedical research.[117] As opposed to prognostic or predictive models, diagnostic models focus on the current state of the patient, and model accuracy is concerned with discrimination or the ability to separate those with and without disease. The goal of diagnosis and diagnostic models is to accurately classify patients into their true disease states. Thus, diagnostic models can be used to assess whether or not skeletal muscle quality measures can meaningfully classify older adults with cancer and comorbid diabetes as frail or non-frail. I used the following diagnostic model methods:

Measures of Validity

Measures of validity were used to report the performance of various skeletal muscle quality cut-points in identifying frailty. As SMD is a continuous measure, we reported sensitivity and specificity, for gender-specific quartile cut-off points in identifying frailty. These measures of validity were calculated for the diabetic and non-diabetic subsets and for each gender. We also reported measures of validity for the Martin *et al*. 2013 and Martin *et al*. 2018 criteria defined in **Table 10**.[110,111]

Additionally, we evaluated modification of the sensitivity and specificity. Using the gender-specific quartile cut-off points and the categorical Martin *et al*. 2013 and Martin *et al*. 2018 criteria, we assessed modification for each gender based on diabetes status to evaluate whether diabetes impacted measures of validity.[118] We reported sensitivity differences and

specificity differences and calculated 95% confidence intervals for the differences using 2,000 bootstrap replicates. This method allowed evaluation of whether or not SMD, as a screening tool for frailty, performed differently for diabetics versus nondiabetics.[118] As this dissertation was focused on classifying frailty and preventing treatment adverse events, we prioritized comparing the sensitivity estimates of different low-SMD categorizations. This allowed us to identify SMD categorizations that maximize the proportion of **true-positives** (sensitivity) and minimize the proportions of **false-negatives** (1-sensitivity). For this aim, false-negatives were frail patients who would be incorrectly identified as being non-frail (robust or pre-frail) based on imaging metric results. These patients may consequently be prescribed an aggressive treatment course that puts them at risk for treatment-related adverse events.

In epidemiological research, there are several settings where SMD categories could be of use including as a stratification variable, confounder or longitudinal assessment of frailty as an outcome. The relative importance of different validity measures depends on the intended use. For this research, SMD was as a proposed screening tool for follow-up GA. Because the goal of frailty screening is to correctly classify all persons with frailty, sensitivity was preferred over specificity.[119] Sensitivity is the primary consideration in settings where the benefits of identifying more true-positives outweigh the negative consequences of including more false-negatives. Below are two cases that are relevant to this work where prioritizing sensitivity is important:

A.) Reducing costs from a more accurate measurement tool. While it is recommended that GA be performed for all older adults receiving chemotherapy, a full GA is time- and resource-intensive as it may take up to two hours to complete and may require multiple health evaluators (e.g., physicians, physical therapists, social workers).[5,38,41] Completing a full GA for every older adult patient undergoing chemotherapy is therefore difficult. As an alternative to performing GA for all patients, muscle metrics derived from CT imaging could be used preliminarily to flag

patients who should undergo full GA. CT scans are already routinely taken for cancer diagnosis and staging; therefore, most patients with solid tumors should theoretically have scans available before treatment. Although some time is involved in processing the L3 scan for muscle measurements, with freely available software, SMD can be estimated for each patient in less than 10 minutes. Therefore, these metrics can be used to efficiently screen for frailty, and full GA can be reserved for patients who test positive on the screening tool.

In this setting, costs are reduced by performing full GA only on true-positives (frail patients who screen positive on SMD) and on false-positives (non-frail patients who screen positive on SMD). A low-SMD categorization that maximizes sensitivity ensures that more truly frail patients are detected and flagged for further frailty assessment. More importantly, definitions with high sensitivity minimize the occurrence of false-negatives (frail patients who screen negative on SMD); these frail patients are not indicated for follow-up assessment and risk being treated aggressively.

It should be noted that specificity was not negligible for assessing screening performance. Low-SMD definitions that prioritize specificity maximize detection of true-negatives (non-frail patients who screen negative on SMD) and minimize false-positives (non-frail patients who screen positive on SMD). Oncology clinics are often busy and minimizing false-positives reduces the number of GAs that are conducted for non-frail patients who may not need it. However, in this setting of using SMD as a screening tool before GA, false-positives do not carry as great of a risk of aggressive treatment assignment as compared to false-negatives. False-positives would undergo GA and be confirmed to be non-frail with treatment assigned accordingly. False-negatives would not be flagged for follow-up GA and may receive overly aggressive treatment that puts them at risk for treatment complications and intolerance. Therefore, for patient safety and minimizing false-negatives, sensitivity should be prioritized over specificity.

B.) Enhancing study inclusiveness. Prioritizing sensitivity is also recommended in settings where it is important to capture the full spectrum of patients with disease.[119] There may be heterogeneity amongst frail patients, and by selecting cut-off points that maximize sensitivity, we ensured that a broad range of frail patients were categorized as frail rather than only the most severe cases.

Receiver Operating Characteristic Curves

The receiver operating characteristic (ROC) curve is the most common measure of discrimination that uses the whole range of possible cut-points.[117] In diagnostic models, the ROC curve is a plot of sensitivity (true-positive fraction, TPF) versus 1-specificity (false-positive fraction, FPF) for the range of diagnosis test scores.[120] The area under the ROC curve (AUC), or c-statistic or c-index, is an overall summary of diagnostic accuracy across the range of cut-off points. For continuous diagnostic data, the nonparametric estimate of AUC is the Wilcoxon rank-sum test. For our study, this was calculated as the proportion of all possible pairs of frail and non-frail patients for which the frail patient muscle quality score was worse than the non-frail patient's score plus half the proportion of score ties. AUC scores generally range from 0.5 to 1.0 with 0.5 indicating that the diagnostic test performs as good as random chance at classifying non-diseased and diseased patients, and 1.0 indicating that the test performs with perfect discrimination or accuracy. For Aim 1, we plotted the ROC curve and estimated the AUC for each gender-diabetes subsets.

Positive and Negative Likelihood Ratios

Likelihood ratios summarize screening accuracy for SMD cut-off points and low-SMD criteria. Positive and negative likelihood ratios (LR+ and LR-) measure the relative degree of support a positive or negative screening test result would give to two competing hypotheses: presence versus absence of frailty given screening criteria.[121] Thus, each cut-off criteria has its

own LR+ and LR- which summarizes how much more likely patients with frailty are to have a positive or negative result compared to patients without frailty.[121] For men and women, and for each gender-diabetes subgroup, we calculated LR+ and LR- and estimated 95% confidence intervals (see **Figure 4**). Although LR+ above 10 and LR- below 0.1 are thresholds conventionally considered to be strong evidence for ruling in or ruling out diagnoses,[121,122] we compared likelihood ratio estimates among the gender-diabetes subsets. Further, LR+ and LR- can be applied to understand how much a positive or negative SMD screening result could change a clinician's evaluation of frailty probability.[121] We present scenarios of how positive and negative screening results could change clinical evaluation of a patient with 33% pre-screening probability of frailty (sample calculations provided in **Figure 5**).[121] Thirty-three percent was selected based on clinical expectations for frailty prevalence in a patient population with gastrointestinal cancers. **Table 13** summarizes the methods used in Aim 1.

Figure 4. Measures for Evaluating Skeletal Muscle Density (SMD) Screening Performance

Screening Result	Truth: Frailty present	Truth: Frailty not present
Low SMD	A (true positives)	B (false positives)
Normal SMD	C (false negatives)	D (true negatives)

Measures of validity

Sensitivity: Proportion of patients with frailty that are identified as being at-risk for frailty based on SMD screening results. Also referred to as true-positive fraction $\frac{A}{A+C}$

Specificity: Proportion of patients without frailty that are identified as being non-frail based on SMD screening results. Also referred to as false-positive fraction $\frac{D}{B+D}$

Positive predictive value: Proportion of patients who screen positive for frailty based on low SMD who are truly frail. $\frac{A}{A+B}$

Negative predictive value: Proportion of patients who screen negative for frailty based on normal SMD who are truly not frail. $\frac{D}{C+D}$

Calculation of likelihood ratios:

Positive likelihood ratios (LR+) = $\frac{sensitivity}{(1-specificity)}$ or $\frac{\Pr(positive\ test \mid frail\ status)}{\Pr(positive\ test \mid non{-}frail\ status)}$

Negative likelihood ratios (LR-) = $\frac{(1-sensitivity)}{specificity}$ or $\frac{\Pr(negative\ test \mid frail\ status)}{\Pr(negative\ test \mid non{-}frail\ status)}$

LR+ = positive likelihood ratio, LR- = negative likelihood ratio, Pr = probability, SMD = skeletal muscle density.

Figure 5. Calculations of post-screening frailty probability using likelihood ratios

Calculation steps	Equations	Scenario: LR+ = 10.0	Scenario: LR- = 0.1
Pre-screen probability	p_1	0.333	0.333
pre-screen odds (o_1)	$p_1 \,/\, (1 - p_1)$	0.499	0.499
post-screen odds (o_2)	$o_1 \times$ likelihood ratio	4.992	0.049
Post-screen probability (p_2)	$o_2 \,/\, (1 + o_2)$	0.833	0.048

Interpretation: Given selected cut-off criteria and 33% pre-screening frailty probability, patients who screen positive on SMD have a 83% post-screening probability of frailty while patients who screen negative on SMD have a <5% post-screening probability of frailty.

LR+ = positive likelihood ratio, LR- = negative likelihood ratio, SMD = skeletal muscle density.

Table 13. Organization of Aim 1 Methods

Method	Muscle Quality Operationalization	Frailty Operationalization
Scatterplot and unadjusted linear regression	Continuous SMD	Continuous frailty score
Diagnostic models—ROC curves	All possible cut-off points for continuous SMD	Frail vs. non-frail (pre-frail or robust) Sensitivity analysis: Frail or pre-frail vs. robust
Diagnostic models—Sensitivity and specificity	Gender-specific quartile cut-off points	Frail vs. non-frail Sensitivity analysis: Frail or pre-frail vs. robust
Diagnostic models—Modification of sensitivity and specificity by diabetes status	Gender-specific quartile cut-off points	Frail vs. non-frail Sensitivity analysis: Frail or pre-frail vs. robust
Positive and negative likelihood ratios	Gender-specific quartile cut-off points	Frail vs. non-frail Sensitivity analysis: Frail or pre-frail vs. robust

Aim 2—Latent Class Analysis

Latent class analysis (LCA) is a statistical procedure that is used to detect heterogeneity in a population sample, and it can be used to identify qualitatively different subgroups within a population.[123] As a form of person-centered mixture modeling, LCA uses study participant responses and categorical indicator variables to identify latent (or unobserved) groups that share patterns of responses to observed variables.[124] The underlying assumption in LCA is that membership in antecedent latent classes can explain patterns of survey responses, categorial indicator variables, or scales.[124,125] It uses cross-classification of responses on indicator variables to identify each unique response combination that exists within a dataset or population.[123] Then latent class models with 1, 2, 3… etc. classes are fit to the data and posterior probabilities for each class are estimated for respondents. The clustered characteristics are considered independent conditional on each latent class. We conducted LCA using the 13 impairment indicators to model latent class probabilities (**Table 11**). The number of latent classes used to fit the data was determined by evaluating model iterations containing 1 to 8 classes. Models were evaluated quantitatively and qualitatively using the following criteria: 1.) lower values for Akaike information criteria (AIC), Bayesian information criteria (BIC), and adjusted Bayesian information criterion (aBIC); 2.) bootstrapped likelihood ratio tests (LRTs); 3.) entropy; and 4.) based on substantive interpretation of classes.[126] Bootstrapped LRTs test the null hypothesis that modeling *k* classes is adequate compared to modeling *k + 1* classes. We evaluated bootstrapped LRT p-values using a 0.05 significance level with significant results indicating that the larger model with *k + 1* classes fit the sample better than the smaller model. Entropy assessed discrimination and values of 0.8 or higher indicated acceptable class separation[125]. We assigned patients to a latent class based on their maximum posterior class membership probability. To facilitate interpretation and labeling of each class, we assessed domain impairment probabilities for each latent class and incorporated clinical input. For the resulting latent classes and for the overall patient sample, we reported patient characteristics

using counts and percentages for categorical characteristics and using median, first quartile and third quartile for continuous characteristics.

Aim 2—1-Year Mortality

For the identified latent impairment classes and for the frailty categories, we evaluated 1-year mortality using Kaplan-Meir curves, and risk estimates, and 95% confidence intervals. We additionally compared risk estimates between impairment classes and between frailty categories using risk differences, risk ratios, and 95% confidence intervals for the contrasts. In secondary analyses evaluating 1-year mortality in the subgroups of patients with high- vs. low-risk cancers and in the patients with stage IV vs. stage I-III cancer, we evaluated risk differences between the subgroups for each latent class and calculated 95% confidence intervals for the differences.

Ancillary and Sensitivity Analyses

Evaluation of pre-treatment patients**.** For Aim 1 we conducted analyses among patients who were considered “pre-treatment”. These patients may have had previous chemotherapy lines, but were considered pre-treatment at the time of CARE tool completion and before they planned to receive their current chemotherapy line.

Alternative categorizations of frailty**.** Aim 1 assessed frailty as an outcome. Categorizations for these analyses were focused on identifying frail patients vs. pre-frail or robust patients. However, patients that meet criteria for pre-frailty are also meaningful to assess because they are not visibly frail and considerations for clinical decisions may be different from robust patients. In sensitivity analyses, we assessed a frailty categorization that combined frail and pre-frail patients.

3.7. Human Subjects

This study included health data of older adults (aged ≥60 years) collected as part of a registry; patients submitted a patient-reported form and consented to have CT scans processed and patient records abstracted for study purposes. With UNC-affiliated co-investigators (JL, CP, JB, TS) listed as co-investigators, the principal investigator submitted an Institutional Review Board (IRB) application to the Office of Human Research Ethics at the University of North Carolina at Chapel Hill. The study was approved (Study # 20-3360) with a notice of IRB exemption in March 2021. Along with an informal data use agreement signed by the principal investigator, the UNC IRB notice was submitted as part of an amendment to the original CARE Registry IRB study submission at UAB. UAB's Office of the Institutional Review Board for Human Use approved the revision/amendment in April 2021. The de-identified dataset was stored on a password-protected desktop that met the security requirements determined by the UNC Office of Human Research Ethics.

CHAPTER 4: SKELETAL MUSCLE DENSITY PERFORMANCE FOR SCREENING FRAILTY IN OLDER ADULTS WITH CANCER AND IMPACTS OF DIABETES: THE CARE REGISTRY

4.1. Introduction

With half of new US cancer diagnoses occurring among adults age 65 or older, cancer is broadly considered to be a disease of aging.[1] Because chronological age is an imperfect marker of health deficits, one complexity in treating older adults with cancer is in identifying those who may be vulnerable to adverse outcomes as a result of accrued comorbidities, conditions, and functional deficits.[3] Frailty is one medical concept that characterizes the most vulnerable subset of older patients.[21] Patients with frailty are in a state of increased vulnerability due to accrued impairments in multiple body systems and health domains, and impairments confer a diminished ability to respond to even mild stressors.[21]

Both cancer itself and cancer treatment can be significant stressors, and frailty has been shown to be associated with adverse events following treatment with surgery or chemotherapy.[127] In acknowledging the clinical value of identifying frailty, the American Society of Clinical Oncology (ASCO) recommends using a clinical tool called geriatric assessment to identify vulnerabilities or geriatric impairments that are not regularly captured in oncology assessments.[5] These clinical evaluations include assessment of function, comorbidity, falls, depression, cognition, and nutrition; and other health areas may be assessed such as vision, hearing, urinary continence, osteoporosis, polypharmacy, and socioenvironmental circumstances.[38] Unfortunately, a recent ASCO task force survey shows that physicians in oncology practices do not frequently use these tools, citing a lack of time, and resources as barriers to implementing use.[4] While modified geriatric assessments have been designed to be

shorter and more streamlined, resources are still required for assessment and grading, and evaluations are dependent on patient responses.[6]

As an alternative to patient-reported methods and clinical frailty evaluations, skeletal muscle metrics from computed tomography (CT) scans have been shown to be associated with frailty[49]. With automated software, these metrics can be calculated with minimal additional resources, and they may also be available for most patients diagnosed with cancer as CT imaging is routinely conducted for initial staging. Beyond muscle volume, metrics capturing muscle composition, specifically skeletal muscle density (SMD), have been shown to be associated with elevated mortality in patients with gastrointestinal cancers.[47] SMD is an indirect indicator of excessive adipose infiltration into muscle tissue—a pathological phenomenon termed myosteatosis— and low SMD has been shown to be associated with hospitalizations and chemotherapy toxicities.[16]

Previous research has demonstrated that CT-derived SMD is correlated with frailty among older adults with cancer[49]; however, SMD utility for patients with comorbid diabetes is unknown. Diabetes and obesity are associated with increased risk of many cancers and poor prognosis, and due to the increased prevalence of these and other aging-related factors, older adults living with cancer and diabetes represent a growing subpopulation.[128,129] Based on longitudinal evidence from the Health, Aging and Body Composition (Health ABC) Study, diabetes may be associated with greater 5-year increases in intermuscular fat in older adult men, but it may not impact older adult women.[17] Because of proposed links between diabetes, insulin resistance, and myosteatosis[130], older adults with cancer and diabetes may have lower muscle density at the point of cancer treatment planning. This may impact the performance of CT-derived SMD in screening for frailty.

The objective of this study was to assess the performance of SMD as a screening tool for frailty in older adults with cancer and to compare performance between men and women

with and without comorbid diabetes. We additionally evaluated the clinical utility of positive and negative SMD results on downstream projections for patient frailty.

4.2. Methods

4.2.1. Data Source and Study Population

This cross-sectional study used data from the Cancer & Aging Resilience Evaluation (CARE) Registry, an ongoing single-site registry of older adult cancer patients at the University of Alabama at Birmingham (UAB)[6]. The registry's overarching goal is to evaluate implementation of geriatric assessment in the routine care of older adults with cancer referred for initial consultation. All patients (≥60 years) with a new patient visit scheduled with the UAB gastrointestinal oncology team were approached to participate. Briefly, at appointment check-in, patients were provided a paper questionnaire (CARE tool) to be completed in the waiting room and collected during nurse triage. The clinical team reviewed questionnaire responses before clinical consultation; and after consultation, patients were approached for consent to have their data stored in the registry for research purposes. All persons gave their informed consent prior to their enrollment and data storage in the registry. CT scans for patients with cancers indicated for internal imaging were stored for the registry if they were taken within ±60 days of CARE tool completion.

4.2.2. Frailty Index

Frailty was assessed using the CARE tool. This completely patient-reported geriatric assessment was adapted from the Cancer and Aging Research Group (CARG) geriatric assessment developed by Hurria and colleagues[45] and was tailored to survey a gastrointestinal cancer population.[6] Across 82 items, patients reported on all essential domains of the geriatric assessment including functional status, physical function, nutrition, health-related quality of life, social support, social activities, psychological status, cognitive function, comorbidities and

polypharmacy. Responses were recorded on scantron forms, and a trained clinical data analyst uploaded forms into the registry database. Frailty was defined based on the principles of deficit accumulation using 44 health deficit items in the CARE tool; items were coded as indicating the presence of deficit ('1'), absence of the deficit ('0'), or intermediate responses (e.g., 'sometimes' or 'maybe'; '0.5')[7-9]. Based on coded items, an index was developed, and patient frailty scores were assigned to represent the overall proportion of deficits (range 0-1)[114,115]. Frailty scores were only calculated for patients who responded to ≥24 of the 44 health deficit items.[112-114]. Using previously defined thresholds for frailty indices, frailty scores were categorized to identify patients considered robust (0-0.2), pre-frail (0.2-0.35), or frail (>0.35).[115] For main analyses, patients were categorized as frail vs. non-frail (pre-frail or robust), and sensitivity analyses explored the dichotomization of frail or pre-frail status versus robust.

4.2.3. Diabetes

Diabetes status was self-reported using the Older Americans Resources and Services (OARS) comorbidity measure that is part of the CARE tool.[131-133] Patients were asked if they have diabetes at the present time (yes/no), and if illness interferes with their activities (a great deal/somewhat/not at all).

4.2.4. Body Composition Analysis

Abdominal CT images taken within ±60 days of CARE tool completion were acquired, and transverse sections at the third lumbar vertebrae (L3) were identified, extracted, and analyzed with automatic tissue segmentation using a proprietary algorithm (https://www.voronoihealthanalytics.com)[108]. From 2D single-slice images, total tissue area was calculated for four tissue types: skeletal muscle, bone, subcutaneous adipose tissue, and visceral adipose tissue. SMD was also calculated by software using the average pixel

attenuation for the skeletal muscle image area (Hounsfield Units, HU). Images were reviewed by a trained research technician for image quality and processing.

For primary analyses, we used the continuous form of SMD and evaluated gender-specific quartile cut-off points. In secondary analyses, we categorized patient SMD results (low vs. normal SMD) based on two criteria identified in a recent systematic review.[47] (1) Martin *et al*. 2013[110] determined cut-off points for predicting survival: low-SMD criteria <41 HU (BMI <25) and <33 HU (BMI ≥ 25). (2) Martin *et al*. 2018[111] determined cut-off points for predicting hospital length of stay: criteria for women: <39.6 HU (age <50 yrs.), 36.0 HU (50-59 yrs.) 31.4 HU (60-69 yrs.) , 27.8 HU (70-79 yrs.), 24.8 HU (≥80 yrs.); and for men: <42.0 HU (age <50 yrs.), <37.6 HU (age 50-59 yrs.), < 32.9 HU (age 60-69 yrs.), <29.7 HU (70-79 yrs.), <28.1 HU (≥80 yrs.). These criteria and were defined in older adults with stage I-IV, gastrointestinal cancers.

4.2.5. Sample Characteristics

Race (White, Black or African American, Native American or Alaskan, Asian, Native Hawaiian, other), ethnicity (Hispanic or Latino, non-Hispanic), education level (less than high school, high school graduate, associate/Bachelors, advanced degree), and marital status (single, widowed/divorced, married) were self-reported in the CARE tool. The race and ethnicity items were taken to represent social constructs and reflect racial self-classification, one race dimension characterized by closed-ended, self-identification questions that fit a racial schema for data collection.[134] Age and gender were extracted from electronic health records by a trained research assistant along with other information including height and weight (measured ≤2 weeks before treatment start date) for calculation of body mass index (BMI), cancer type and stage, current chemotherapy treatment line (1, 2-4, or ≥5), and chemotherapy treatment phase (pre-treatment, during, or post-chemotherapy). In the health records, age was self-reported as an integer and captures chronological age. Gender (male or female) was self-reported by patients at the time of registration with UAB Medicine and represents self-identified sexual

identity. Patient BMI was categorized (underweight, normal, overweight, or obese), and we incorporated Asian- (≥22.2 and ≥26.9 kg/m^2) and Black-specific (≥23.4 and ≥28.1 kg/m^2) cut-off points for overweight and obese based on prior work assessing ethnic differences in BMI and diabetes risk.[135] Patient function was also described using CARE tool responses for the following measures: Eastern Cooperative Oncology Group (ECOG) performance status (0-1, ≥2, or unknown), instrumental activities of daily living (IADL; any impairment, none, or unknown), and activities of daily living (ADL; any impairment, none, or unknown).

4.2.6. Statistical Analysis

For the present study, we conducted a complete patient analysis by excluding patients missing CT images taken within the ±60-day window (n=613) and patients missing frailty score or diabetes status on the CARE tool (n=154). We additionally excluded patients with missing or pending information on cancer stage (n=132) and patients with cancer stage 0 (n=3). **Figure 6** depicts the inclusion flow chart for the study sample.

For each subgroup of women and men with and without diabetes, categorical patient characteristics were described using counts and percentages, and continuous characteristics were categorized or described using median, first quartile (Q1) and third quartile (Q3). For each gender and for each gender-diabetes subgroup, SMD was described using histograms, median, Q1 and Q3. The crude association between continuous SMD and frailty score was described using scatterplots and unadjusted linear regression with R^2 values to compare model fit.

Frailty scores were then categorized as frail vs. non-frail (robust or pre-frail), and we conducted the following diagnostic model methodologies.[136] First, we plotted receiver operating characteristic (ROC) curves and 95% confidence bands for the overall male and female samples and for each gender-diabetes subset using the pROC R package.[120] For each ROC curve, diagnostic accuracy across the range of SMD cut-off points was summarized with the

area under the ROC curve (AUC) and the 95% confidence intervals were calculated with 2,000 bootstrap replicates. The second diagnostic method focused on sensitivity and specificity of select cut-off points (see **Figure 4**). For each gender and for each gender-diabetes subgroup, we calculated separate sensitivity and specificity estimates and 95% confidence intervals. For primary analyses, we evaluated gender-specific, SMD quartile cut-off points for low SMD (Q1, median, Q3) which represented screening criteria that would respectively flag 25%, 50%, and 75% of patients for follow-up frailty assessment. We further evaluated whether diabetes status modified sensitivity and specificity estimates by calculating differences in sensitivity and specificity between patients with and without diabetes. 95% confidence intervals for the difference estimates were produced using standard errors from bootstrapped sensitivity and specificity results (2,000 replicates).[137] In secondary analyses, we assessed patients who had not started chemotherapy by the time of CARE tool completion ("pre-treatment"), and we evaluated the Martin *et al*. 2013[110] and the Martin *et al*. 2018[111] low-SMD criteria.

Beyond sensitivity and specificity, we calculated likelihood ratios to further summarize screening accuracy for SMD cut-off points and low-SMD criteria. Positive and negative likelihood ratios (LR+ and LR-) measure the relative degree of support a positive or negative screening test result would give to two competing hypotheses: presence versus absence of frailty given screening criteria.[121] Thus, each cut-off criteria has its own LR+ and LR- which summarize how much more likely patients with frailty are to have a positive or negative result compared to patients without frailty.[121] For men and women, and for each gender-diabetes subgroup, we calculated positive likelihood ratios and estimated 95% confidence intervals (see **Figure 4**). Although LR+ above 10 and LR- below 0.1 are thresholds conventionally considered to be strong evidence for ruling in or ruling out diagnoses,[121,122] we compared likelihood ratio estimates among the gender-diabetes subsets. Further, LR+ and LR- can be applied to understand how much a positive or negative SMD screening result could change a clinician's evaluation of frailty probability.[121] We present scenarios of how positive and negative screening

results could change clinical evaluation of a patient with 33% pre-screening probability of frailty (sample calculations provided in **Figure 5**).[121] Thirty-three percent was selected based on clinical expectations for frailty prevalence in a patient population with gastrointestinal cancers. Finally, we conducted sensitivity analyses evaluating the classification of frail or pre-frail status versus robust. Analyses were conducted using SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC) and R statistical software version 4.1.1. (Comprehensive R Archive Network, CRAN). The CARE registry was approved by the UAB Office of Institutional Review Board and all participants provided written consent prior to their enrollment and data storage in the registry. This specific study protocol was exempted from institutional review board review by the University of North Carolina at Chapel Hill (UNC-CH) Office of Human Research Ethics and was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

4.3. Results

From July 2017 until November 2021 there were 1,526 patients who consented to have their data stored for the CARE registry. After exclusions, 872 patients were included in the final study sample (**Figure 6**). The prevalence of diabetes in the included study sample was 27% in women and 28% in men with nearly one third of patients with diabetes reporting illness that interfered with their activities (n=31, 34% of women with diabetes; n=47, 32% of men with diabetes). **Table 14** provides descriptive characteristics of the study sample by gender and diabetes status. The study sample was predominately White/Caucasian with median age near 70 years. Patients predominately had gastrointestinal cancers and were stage III/IV. Most patients completed the CARE tool before starting chemotherapy treatment and planned to receive their first chemotherapy treatment line. Compared to patients without diabetes, patients with diabetes had a greater portion in overweight or obese BMI categories. Frailty was more

prevalent among patients with diabetes, and these patients had slightly more functional deficits based on ECOG, IADLs and ADLs.

Figure 7 displays SMD distributions for men and women in the study sample and for the subgroups of patients with and without diabetes. Q1, median, and Q3 low-SMD cut-off points were <31.0 HU, <38.1 HU, and <44.1 HU for women and <33.1 HU, <39.9 HU, and <47.5 HU (Q3) for men, respectively. Median SMD was 1-HU lower in patients with diabetes compared to patients without, and patients with diabetes had a lower first quartile which is consistent with greater myosteatosis.

Table 15 provides a summary of findings for each method used to evaluate SMD associations with frailty and performance in classifying frailty. **Figure 8** displays scatterplots for the association of SMD with frailty score and fitted slopes using crude linear regression models. For men and women and for each subset of patients with and without diabetes, we observed a negative slope for the association between SMD and frailty score suggesting that patients with lower SMD tended to have higher frailty scores. Compared to all other panels in **Figure 8**, the magnitude of the negative SMD-frailty-score association was greatest for men with diabetes. Additionally, R^2 values for regression models with SMD alone were low for all panels, but greatest for men with diabetes. Secondary analyses evaluating pre-treatment patients were similar to primary analyses, except women with diabetes had a slightly positive slope (**Figure 9**).

ROC curve analyses evaluating the performance of SMD in classifying frailty are presented in **Figure 10** for each gender strata and for each subset of patients with and without diabetes. Although AUC point estimates were >0.50 for all patient subsets, estimates were less than commonly considered cut-offs for good discrimination (<0.80). Men with diabetes had the greatest AUC point estimate compared to other gender-diabetes subsets suggesting that SMD screening performance was best for men with diabetes across all cut-off points. Results from secondary analyses evaluating pre-treatment patients were similar to primary analyses for men overall and for each subset with and without diabetes (**Figure 11**). Secondary results for women

without diabetes were still ≥0.60 (95% CI 0.50-0.70), but results for women with diabetes were more imprecise, and the AUC point estimate dropped to 0.51 (95% CI 0.37-0.65).

Figure 12 presents sensitivity and specificity estimates for gender-specific SMD quartile cut-off points and evaluates modification of sensitivity and specificity by diabetes status. For men and women, Q1 cut-off points had low sensitivity estimates below 0.40 and specificity estimates around 0.80. Median SMD cut-off points had sensitivity estimates close to 0.60 and specificity estimates between 0.50 and 0.60. Q3 cut-off points had sensitivity estimates above 0.80, but specificity estimates were around 0.30. Regarding sensitivity modification for women, sensitivity difference estimates were small and not consistently positive suggesting that diabetes minimally impacted sensitivity estimates for women. For men, sensitivity point estimates for all three cut-off points were greater among the subset with diabetes. Estimated sensitivity differences comparing men with versus without diabetes were greatest for the Q1-cutoff comparison (0.23 [95% CI 0.07 to 0.38]), and difference estimates were smaller for median (08 [-0.07 to 0.24)] and Q3 (0.11 [0.00 to 0.22]) cut-off comparisons. Regarding specificity, diabetes did not impact specificity estimates for men or women. Results were similar in secondary analyses assessing patients in pre-treatment phase (**Figure 13**), except that there was evidence of specificity modification for women when using the Q1 cut-off point (specificity difference = -0.24, -0.42 to -0.06).

Table 16 displays sensitivity, specificity, and likelihood ratio estimates for the SMD quartile cut-off points. Across all cut-off criteria, positive likelihood ratio estimates were less than 2.0 for women (LR+ range: 1.15-1.94; **Figure 14**). For men, positive likelihood ratio estimates were less than 2.0 for all analyses with the exception of the Q1 cut-off in men with diabetes which had the greatest positive likelihood ratio estimate at 2.92 (95% CI 1.74 to 4.91). Based on this result, in a scenario where a man with diabetes has a pre-screening frailty probability of 33% and is being evaluated using the Q1 cut-off criteria, having an SMD that is less than 33.1 HU indicates a “positive” screening result and the frailty probability increases to 59%. The other

positive likelihood ratio results listed in **Table 16** would produce smaller probability increases for their respective patient scenarios.

Negative likelihood ratio estimates for all gender-diabetes subgroups were predominately above 0.5. The lowest negative likelihood ratio estimate was for use of the Q3 cut-off point for men with diabetes (LR- = 0.46, 0.21 to 1.01). Based on this result, in a scenario where a man with diabetes has a 33% pre-screening frailty probability, having an SMD that is greater than 47.5 HU (a "negative" screening result) would decrease the clinical evaluation of frailty probability to 19%. The other negative likelihood ratio results listed in **Table 16** would produce smaller probability decreases for their respective patient scenarios. Likelihood ratio results for pre-treatment patients were similar to primary analyses (**Table 17**).

In secondary analyses using the low-SMD criteria from literature, the Martin *et al*. 2013 criteria had sensitivity estimates between 0.46-0.60 for women and between 0.51-0.58 for men, depending on diabetes status (**Figure 15, Table 18**). Specificity estimates were between 0.58-0.62 for women and between 0.72-0.76 for men. Sensitivity estimates were lower when using the Martin *et al*. 2018 criteria (0.22-0.33 for women and 0.23-0.44 for men), but specificity estimates were higher (0.69-0.86 for women and 0.84-0.85 for men). Similar to primary analyses, diabetes status did not impact sensitivity or specificity estimates for women. For men, estimated sensitivity using the Martin *et al*. 2018 criteria was 0.23 (0.09 to 0.38) greater for men with diabetes. Diabetes status did not impact sensitivity estimates when using the Martin *et al*. 2013 criteria, and there was no modification of specificity estimates for either criterion. Likelihood ratio results using the Martin *et al*. 2013 and Martin *et al*. 2018 criteria were similar to primary analyses with men with diabetes having the greatest positive likelihood ratio estimate (LR+ = 2.39 and 3.06 for the Martin *et al.* 2013 and Martin *et al*. 2018 criteria, respectively) and lowest negative likelihood ratios (LR- = 0.56 and 0.63 for the Martin *et al*. 2013 and Martin *et al*. 2018 criteria, respectively). Analyses in the pre-treatment patient sample were similar to results in the full study sample (**Figure 16, Table 19**). In sensitivity analyses evaluating the

classification of frail or pre-frail status versus robust, ROC curves results were similar to main analyses (**Figure 17**). Sensitivity, specificity, and likelihood ratio estimates were also similar to main analyses (**Table 20**). For both genders, sensitivity point estimates decreased in sensitivity analyses; there were slight increases in specificity for men and small or inconsistent increases in specificity for women.

4.4. Discussion

In this single-site cancer registry, we report that SMD alone poorly discriminated between patients with and without frailty, and screening performance was similar in patients with and without diabetes. We identified cut-off criteria with reasonable estimated sensitivity (i.e., Q3-cut-offs); however, these high cut-off criteria would still miss 15-24% of women with frailty and 11-22% of men with frailty depending on diabetes status; and these criteria would include many false-positive patients due to low specificity. We were unable to identify cut-off points with both sensitivity >0.80 and specificity >0.50, although among the gender-diabetes patient subgroups that we assessed, SMD screening performance and clinical utility may be most promising when used to screen for frailty in men with diabetes.

Previous studies have documented the association of low SMD with mortality[47] and frailty[49] in patients with cancer. This is the first study to use geriatric assessment responses to evaluate SMD screening performance in classifying frail and non-frail older adult patients. We further explored performance based on gender and diabetes status and report that diabetes status did not impact SMD performance for women. One previous cross-sectional study of postmenopausal women similarly reported greater myosteatosis in women diagnosed with type 2 diabetes, and the authors concluded that skeletal muscle fat alone was a poor clinical indicator of functional mobility and strength in their patient sample.[138] Our analyses, which incorporated function, mobility, and other health domains, further suggest that SMD may not optimally classify women with impairments when used alone, but a high SMD cut-off (e.g., Q3

cut-off) could identify the majority of older women with frailty who should undergo further geriatric assessment.

Screening for frailty using CT-derived body composition metrics has benefits over other screening tools designed to identify patients who require full geriatric assessment, such as the G8 screening tool.[139] It is does not require substantial clinical resources to calculate, it can be calculated automatically with software, and it does not rely on patient self-report. Additionally, internal imaging is routinely conducted for many solid tumor cancers for initial diagnosis and staging and is repeated later for disease response assessment and surveillance. Thus, SMD results could be available for many patients at the start of treatment and throughout cancer care. Further, because lean body mass and total adipose tissue are associated with chemotherapy drug clearance and maximum concentrations[99], muscle-composition-based screening has the potential to inform on drug metabolism and risk for severe chemotoxicities.

One limitation to our study was in dichotomizing frailty scores into frail and non-frail categories which combined patients who were robust or pre-frail. Patients with pre-frailty and relatively low SMD therefore contributed to false-positive results and low specificity. This dichotomization was selected to focus on identifying the most vulnerable patients; and sensitivity analyses showed that screening for frail or pre-frail status may improve SMD specificity at the cost of sensitivity. There are also concerns about the generalizability of the CARE registry patient sample as UAB is an academic healthcare site located in southeastern US, and only patients who provided consent were included in the registry. Our study sample was also restricted to patients with available CT images to evaluate skeletal muscle metrics; and many of participants within the registry were excluded as they either had no CT images available or had scans taken at other clinics or >60 days before CARE tool assessment. This is not unexpected as CT scans are not indicated for diagnosing and staging all cancers and are performed only at certain time points. Our results cannot be used to project screening performance and clinical utility for all cancers. Another limitation is in the use of an imperfect

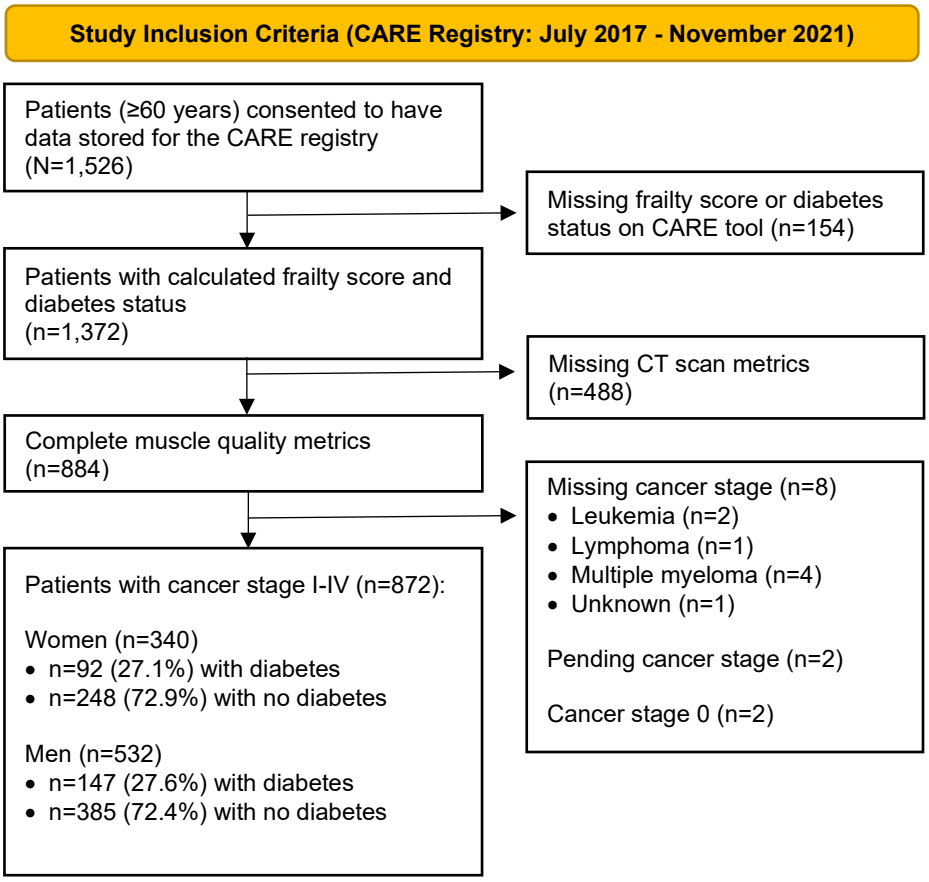
frailty measure—an “alloyed” standard for frailty. Compared to a full geriatric assessment with multiple clinical evaluations and performance-based measures, the CARE tool is a patient-reported questionnaire that lacks physical function measurements. However, the CARE tool has been contoured to identify vulnerabilities in older patients with cancer, and similar cancer-specific frailty assessments from the CARG study have shown good performance in predicting severe and life-threatening chemotherapy toxicities.[113,140] Furthermore, the registry does not capture undiagnosed diabetes, diabetes duration, or treatments which include medications that may be protective against myosteatosis (e.g., metformin) and non-medicated approaches (e.g., diet control and physical activity).[141] We were therefore unable to explore heterogeneity in SMD performance for patients with diabetes or pre-diabetes.

Despite our study limitations, there are a number of strengths. The CARE registry is a rich data source that includes CT scans assessed using an auto-segmentation approach which reduces labor and dependence on manual segmentation. Additionally, the self-reported CARE tool is a highly feasible geriatric assessment which minimized selection biases associated with who is able to complete an evaluation. Further, because patients completed the CARE tool before knowing that responses may be stored for research, reporting biases were minimized.

Our work suggests that there is room for improvement when it comes to SMD screening performance in identifying patients for further frailty assessment, and performance may be similar in patients with and without diabetes. To identify most patients with frailty using SMD alone, a clinic must use high cut-off criteria, but this would flag a large proportion of non-frail patients unnecessarily. More work is needed to understand the clinical and resource impacts of different cut-off criteria such as patient and physician availability and preferences for extensive assessment. Additionally, future research in larger patient samples should continue exploring whether performance is better in specific patient subgroups or if performance improvements are possible using additional geriatric assessment items or clinical data. Future efforts to promote the use of SMD as a screening tool for frailty or as predictor of cancer treatment adverse events

should highlight its utility in men with diabetes as this is a common co-morbid condition in older adults in general and in older adults with cancer.

Figure 6. Inclusion Criteria for the CARE Registry Study Sample (University of Alabama at Birmingham)



CARE = Cancer and Aging Resilience Evaluation, CT = computed tomography.

Table 14. Characteristics of the CARE Registry Study Sample at Recruitment (University of Alabama at Birmingham, 2017-2021, N = 872)

	Female		Male	
	Diabetes n (%)	**No Diabetes n (%)**	**Diabetes n (%)**	**No Diabetes n (%)**
Total, N	92	248	147	385
Age (median, IQR)	68 (64-74)	70 (65-75)	69 (64-73)	68 (64-74)
Race				
White / Caucasian	62 (67.4)	190 (76.6)	111 (75.5)	297 (77.1)
Black / African American	28 (30.4)	55 (22.2)	33 (22.5)	81 (21.0)
Asian	2 (2.2)	1 (0.4)	2 (1.4)	3 (0.8)
American Indian / Alaska Native	0 (0.0)	1 (0.4)	1 (0.7)	0 (0.0)
Other / unknown	0 (0.0)	1 (0.4)	0 (0.0)	4 (1.0)
Educational level				
Less than high school	13 (14.1)	23 (9.3)	20 (13.6)	51 (13.3)
High school graduate	44 (47.8)	114 (46.0)	83 (56.5)	182 (47.3)
Associate/bachelors	27 (29.4)	75 (30.2)	28 (19.1)	80 (20.8)
Advanced degree	7 (7.6)	22 (8.9)	12 (8.2)	45 (11.7)
Unknown	1 (1.1)	14 (5.7)	4 (2.7)	27 (7.0)
Marital status				
Single, never married	7 (7.6)	10 (4.0)	8 (5.4)	27 (7.0)
Widowed / divorced / separated	46 (50.0)	100 (40.3)	21 (14.3)	84 (21.8)
Married	38 (41.3)	126 (50.8)	114 (77.6)	246 (63.9)
Unknown	1 (1.1)	12 (4.8)	4 (2.7)	28 (7.3)
Cancer type				
GI or GI-related	83 (90.2)	195 (78.6)	114 (77.6)	252 (65.5)
Lung	4 (4.4)	21 (8.5)	7 (4.8)	37 (9.6)
Head and neck	0 (0.0)	10 (4.0)	8 (5.4)	34 (8.8)
Urogenital	2 (2.2)	6 (2.4)	5 (3.4)	16 (4.2)
Reproductive	1 (1.1)	8 (3.2)	11 (7.5)	33 (8.6)
Breast	1 (1.1)	1 (0.4)	0 (0.0)	0 (0.0)
Other[a]	1 (1.1)	7 (2.8)	2 (1.4)	13 (3.4)
Cancer stage				
Stage I	13 (14.1)	15 (6.1)	13 (8.8)	30 (7.8)
Stage II	19 (20.7)	41 (16.5)	34 (23.1)	60 (15.6)
Stage III	26 (28.3)	64 (25.8)	37 (25.2)	101 (26.2)
Stage IV	34 (37.0)	128 (51.6)	63 (42.9)	194 (50.4)
Chemotherapy treatment line				
1	66 (71.7)	157 (63.3)	95 (64.6)	230 (59.7)
2-4	3 (3.3)	23 (9.3)	12 (8.2)	45 (11.7)
≥5	17 (18.5)	40 (16.1)	28 (19.1)	62 (16.1)
Unknown	6 (6.5)	28 (11.3)	12 (8.2)	48 (12.5)
Treatment phase				
Pre-treatment	71 (77.2)	171 (69.0)	115 (78.2)	295 (76.6)
During treatment	15 (16.3)	40 (16.1)	12 (8.2)	54 (14.0)
Post-treatment	6 (6.5)	37 (14.9)	20 (13.6)	36 (9.4)
BMI category[b]				
Underweight	4 (4.4)	17 (6.9)	2 (1.4)	20 (5.2)
Normal	20 (21.7)	101 (40.7)	30 (20.4)	130 (33.8)
Overweight	27 (29.4)	72 (29.0)	61 (41.5)	127 (33.0)
Obese	33 (35.9)	42 (16.9)	49 (33.3)	89 (23.1)
Unknown	8 (8.7)	16 (6.5)	5 (3.4)	19 (4.9)

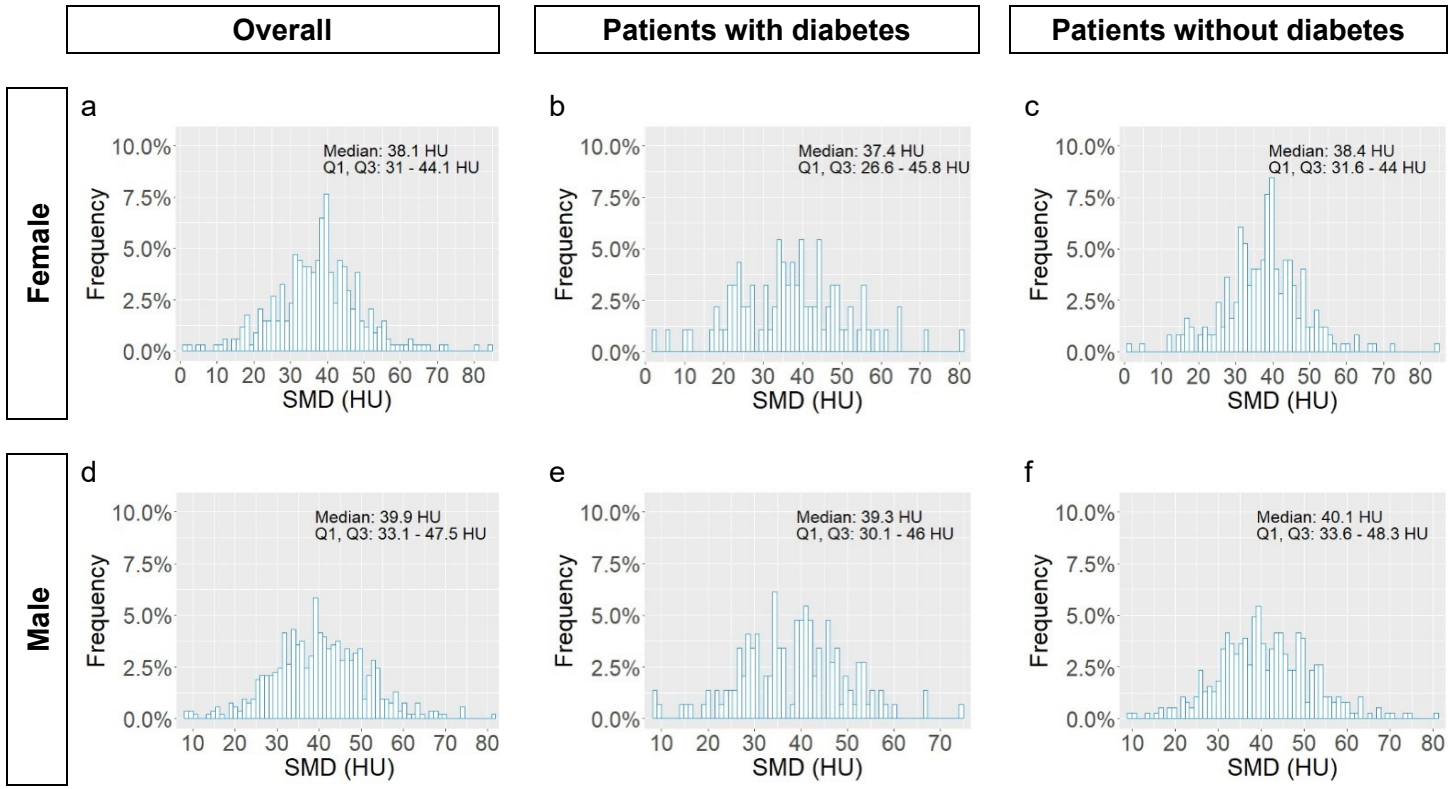
Frailty				
Robust	25 (27.2)	101 (40.7)	32 (21.8)	168 (43.6)
Pre-frail	25 (27.2)	80 (32.3)	53 (36.1)	110 (28.6)
Frail	42 (45.7)	67 (27.0)	62 (42.2)	107 (27.8)
ECOG performance status				
0-1	59 (64.1)	165 (66.5)	93 (63.3)	272 (70.7)
≥2	31 (33.7)	77 (31.1)	50 (34.0)	103 (26.8)
Unknown	2 (2.2)	6 (2.4)	4 (2.7)	10 (2.6)
Any IADL impairment				
Yes	55 (59.8)	142 (57.3)	82 (55.8)	163 (42.3)
No	36 (39.1)	102 (41.1)	60 (40.8)	198 (51.4)
Unknown	1 (1.1)	4 (1.6)	5 (3.4)	24 (6.2)
Any ADL impairment				
Yes	20 (21.7)	37 (14.9)	28 (19.1)	61 (15.8)
No	71 (77.2)	206 (83.1)	118 (80.3)	308 (80.0)
Unknown	1 (1.1)	5 (2.0)	1 (0.7)	16 (4.2)

ADL = activities of daily living, BMI = body mass index, ECOG = Eastern Cooperative Oncology Group, GI = gastrointestinal, HU = Hounsfield units, IADL = instrumental activities of daily living, IQR = interquartile range, SMD = skeletal muscle density.

[a]Other cancers = Cancer of unknown primary, leukemia, lymphomas, melanoma, multiple myeloma, myelodysplastic syndrome, sarcoma, skin cancer (not melanoma), thyroid cancer.

[b]Overweight and obese categories were defined as ≥22.2 and ≥26.9 kg/m2 for patients self-reporting Asian race and as ≥23.4 and ≥28.1 kg/m2 for patients self-reporting Black / African American.

Figure 7. SMD Distribution in the Overall Male and Female Study Samples and by Diabetes Status (CARE Registry, N = 872)



CARE = Cancer and Aging Resilience Evaluation, HU = Hounsfield Units, Q1 = 1st quartile, Q3 = 3rd quartile, SMD = skeletal muscle density.

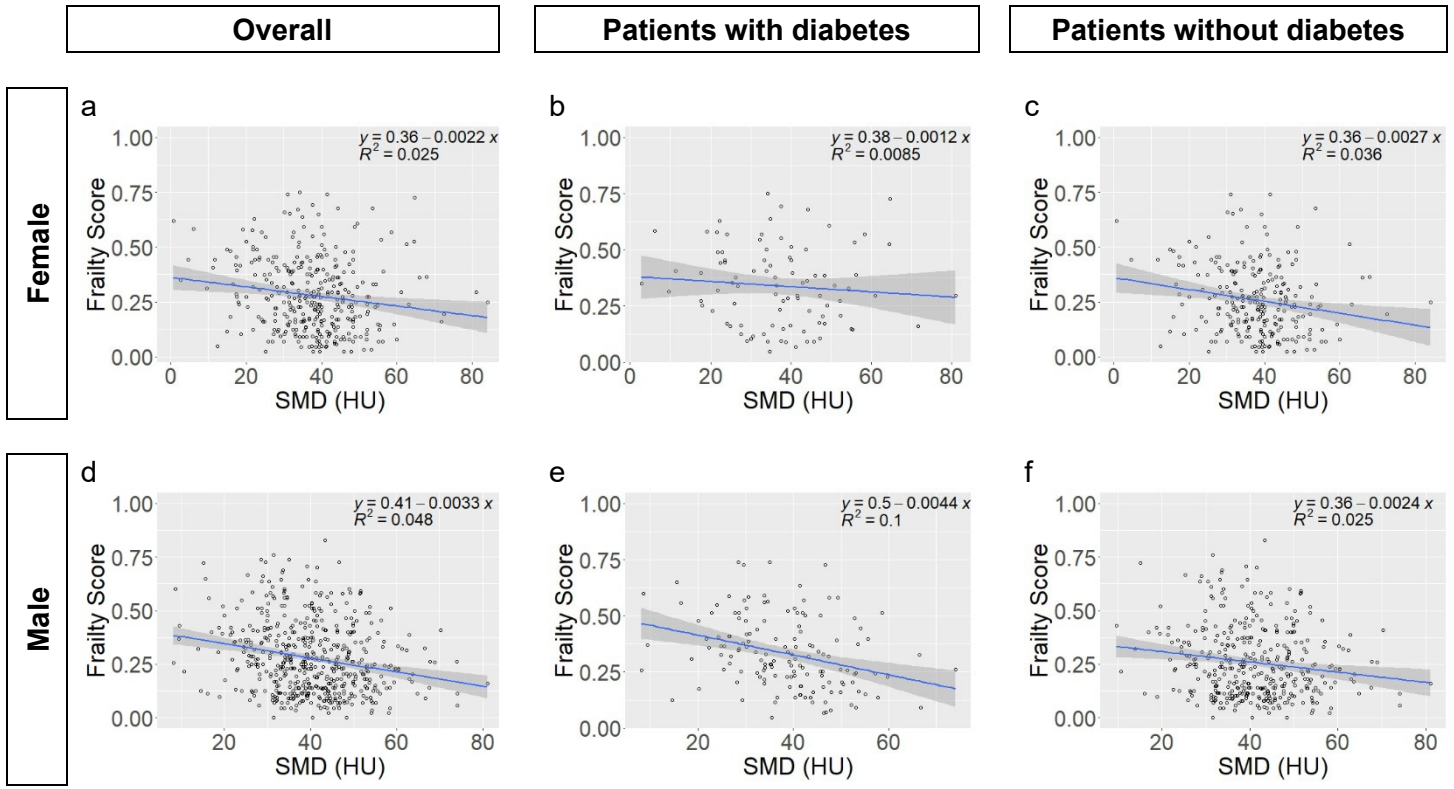
Table 15. A Summary of Methods and Primary Findings Regarding SMD and Frailty in Patients with and without Diabetes

Method	Calculation and Visualization	Interpretations and Findings
Scatterplot with Linear Regression	• Each patient's SMD plotted against their frailty score • Unadjusted linear regression was overlayed to show the modeled association between SMD and frailty score	• The association between SMD and frailty score were assessed from the regression slope **What we found**: • Negative slopes indicated that patients with low SMD tended to have higher frailty score • Slope magnitude was greatest for men with diabetes
Diagnostic Model Approaches		
Receiver Operating Characteristic (ROC) Curve	• Plot of Sensitivity vs. specificity (in classifying frail status) for each possible SMD cut-off point • ROC curves plotted for patients with and without diabetes, separately • Area under the ROC curves (AUC) and CIs were calculated	• AUC point estimates and CIs >0.50 indicate that SMD classifies frail status better than chance across the full range of SMD cut-off points; estimates closer to 1.0 indicate better diagnostic performance ***What we found*** • **Females**: AUC ranged from 0.58-0.62, depending on diabetes status • **Males:** AUC was 0.68 (95% CI 0.59-0.77) for men with diabetes, 0.58 (0.52-0.65) for men without
Sensitivity and Specificity of SMD quartile cut-off points	• Sensitivity and specificity calculated for gender-specific SMD quartile cut-off points (Q1, median, Q3) representing criteria that would flag 25%, 50%, and 75% of men or women, respectively • Measures calculated with 95% CIs in gender and gender-diabetes subsets, separately • Results for each cut-off criteria were plotted on ROC curves	• Cut-off criteria with higher sensitivity identify patients with frailty more accurately • High specificity is also preferred to avoid flagging patients who are not frail (false-positives) • Positive sensitivity or specificity differences with CIs that exclude 0 suggest that performance measures are greater when estimated in patients with diabetes ***What we found:*** • Median-cut off criteria: Sensitivity and specificity were both >0.50

	• Sensitivity differences and specificity differences (patients with diabetes vs. without diabetes) were calculated with CIs	• Q3 cut-off criteria: Sensitivity was >0.80 for men and women, but would still miss 15-24% of women with frailty and 11-22% of men with frailty, respectively; specificity was <0.30 • **Females**: Diabetes status did not impact sensitivity or specificity estimates • **Males**: Sensitivity point estimates were greater when estimated in men with diabetes; differences = 0.23 (0.07 to 0.38), 0.08 (-0.07 to 0.24), 0.11 (0.00 to 0.22) for Q1, median, and Q3 cut-off criteria, respectively
Positive and negative likelihood ratios (LR+ and LR-)	• Proportion of patients with frailty who have positive (or negative) screening results divided by proportion of patients without frailty who have positive (or negative) screening results • LR+ = sensitivity / (1-specificity) • LR- = (1-sensitivity) / (specificity) • Scenario to describe utility: a patient with 33% pre-screening probability of frailty is screened using SMD	• LR+ >10 and LR- <0.1 are considered as strong evidence for ruing in or ruling out frailty ***What we found:*** • **LR+** <2.0 for all gender-diabetes patient subsets, except for Q1 cut-off results for men with diabetes (LR+ = 2.92). Scenario: a man with diabetes has SMD < 33.1 HU (Q1 cut-off); probability of frailty increases from 33% to 59% • **LR-** >0.5 for all gender-diabetes patient subsets, except for Q3-cut-off results for men with diabetes (LR- = 0.46). Scenario: a man with diabetes has SMD ≥47.5 HU (Q3 cut-ff); probability of frailty decreases from 33% to 19%

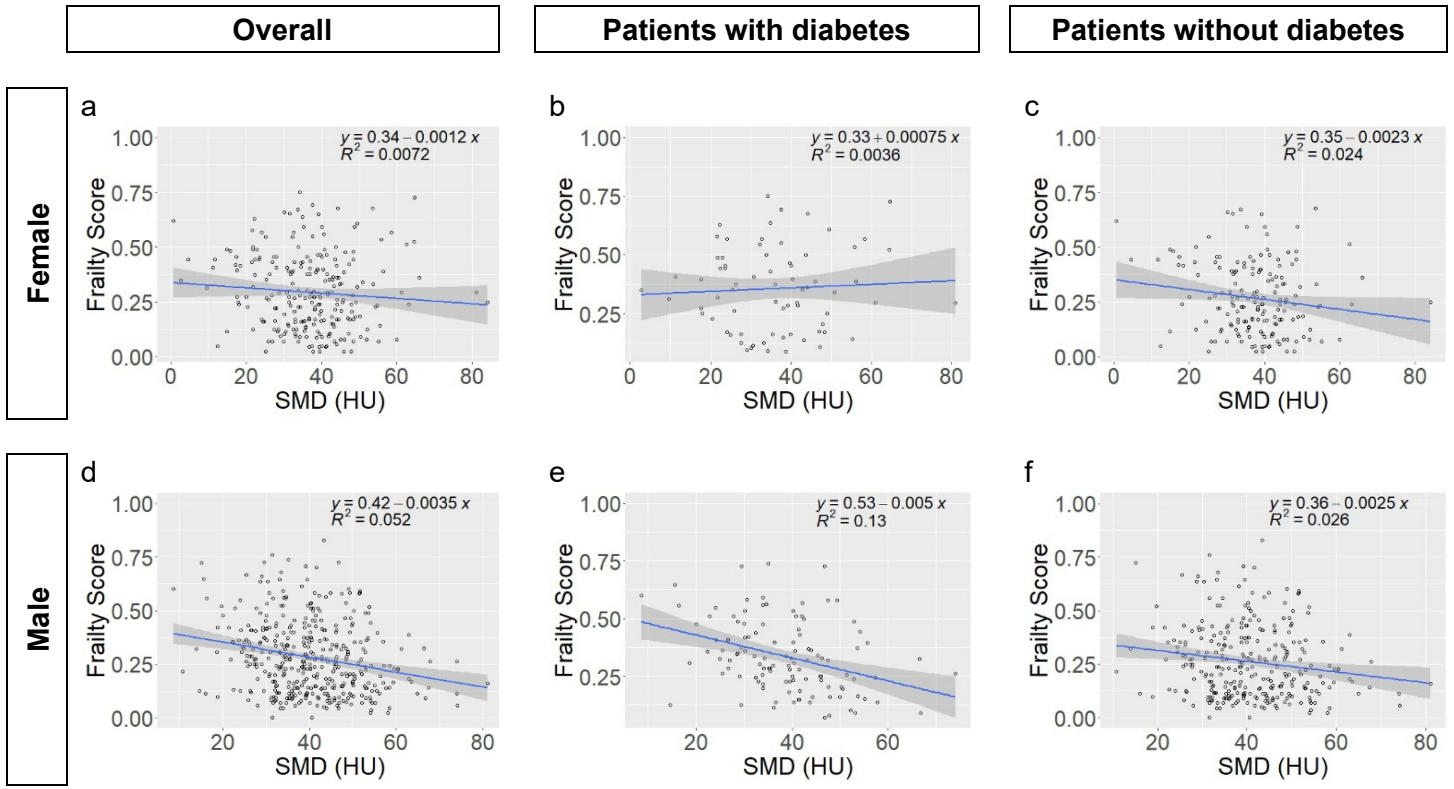
AUC = area under the ROC curve, CI = confidence interval, HU = Hounsfield units, LR+ = positive likelihood ratio, LR- = negative likelihood ratio, Q1 = 1st quartile, Q3 = 3rd quartile, ROC = receiver operating characteristic, SMD = skeletal muscle density.

Figure 8. Scatterplots and Crude Linear Regression for the Association of SMD with Frailty Score in the Male and Female Study Samples and each Diabetes Subset (CARE Registry, N = 872)



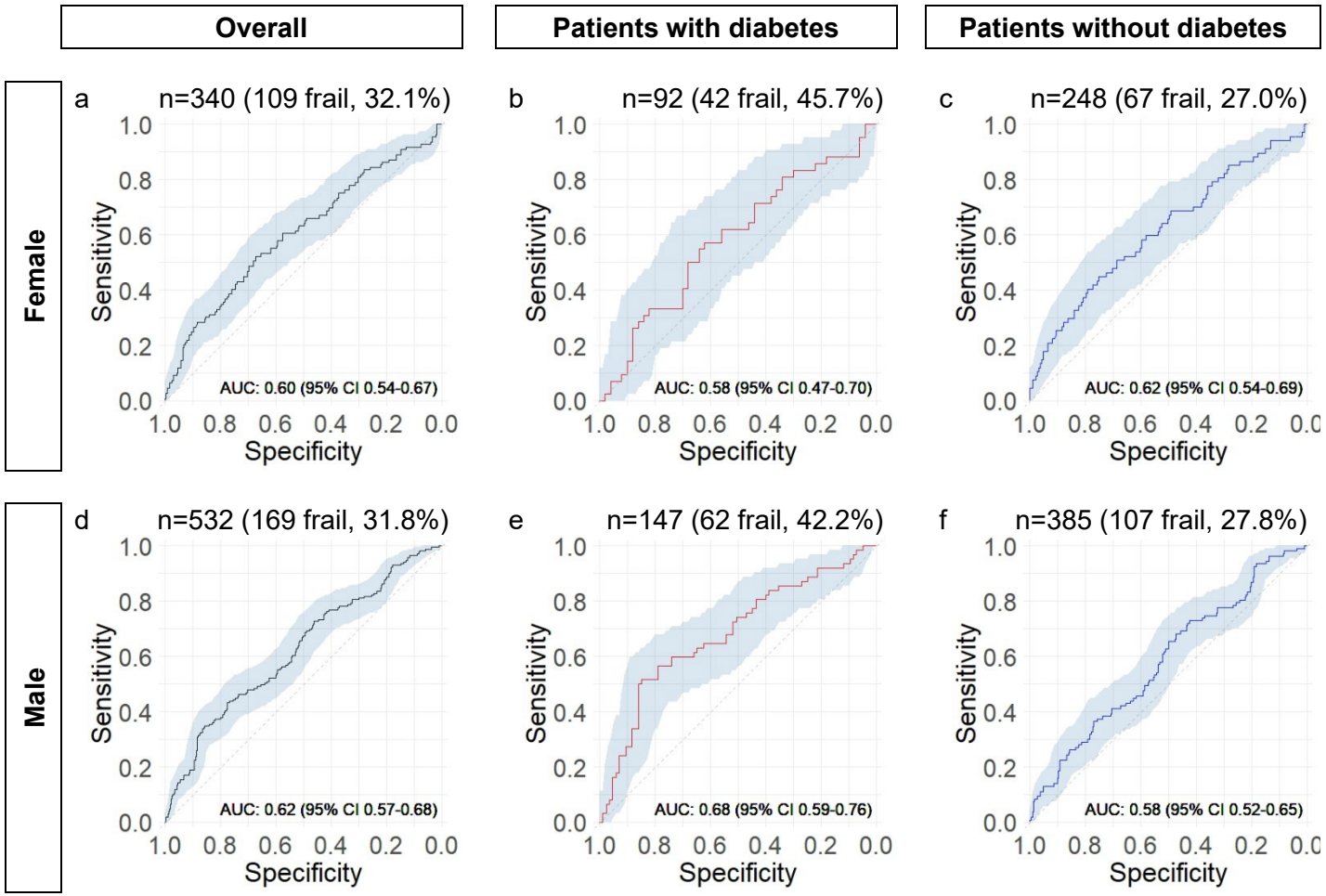
CARE = Cancer and Aging Resilience Evaluation, HU = Hounsfield Units, SMD = skeletal muscle density.
Regression equations were unadjusted linear models for the association of SMD with frailty score.

Figure 9. Secondary Analyses—Scatterplots and Crude Linear Regression for the Association of SMD with Frailty Score in the Male and Female Study Samples and each Diabetes Subset (CARE Registry Pre-treatment Sample, N = 652)



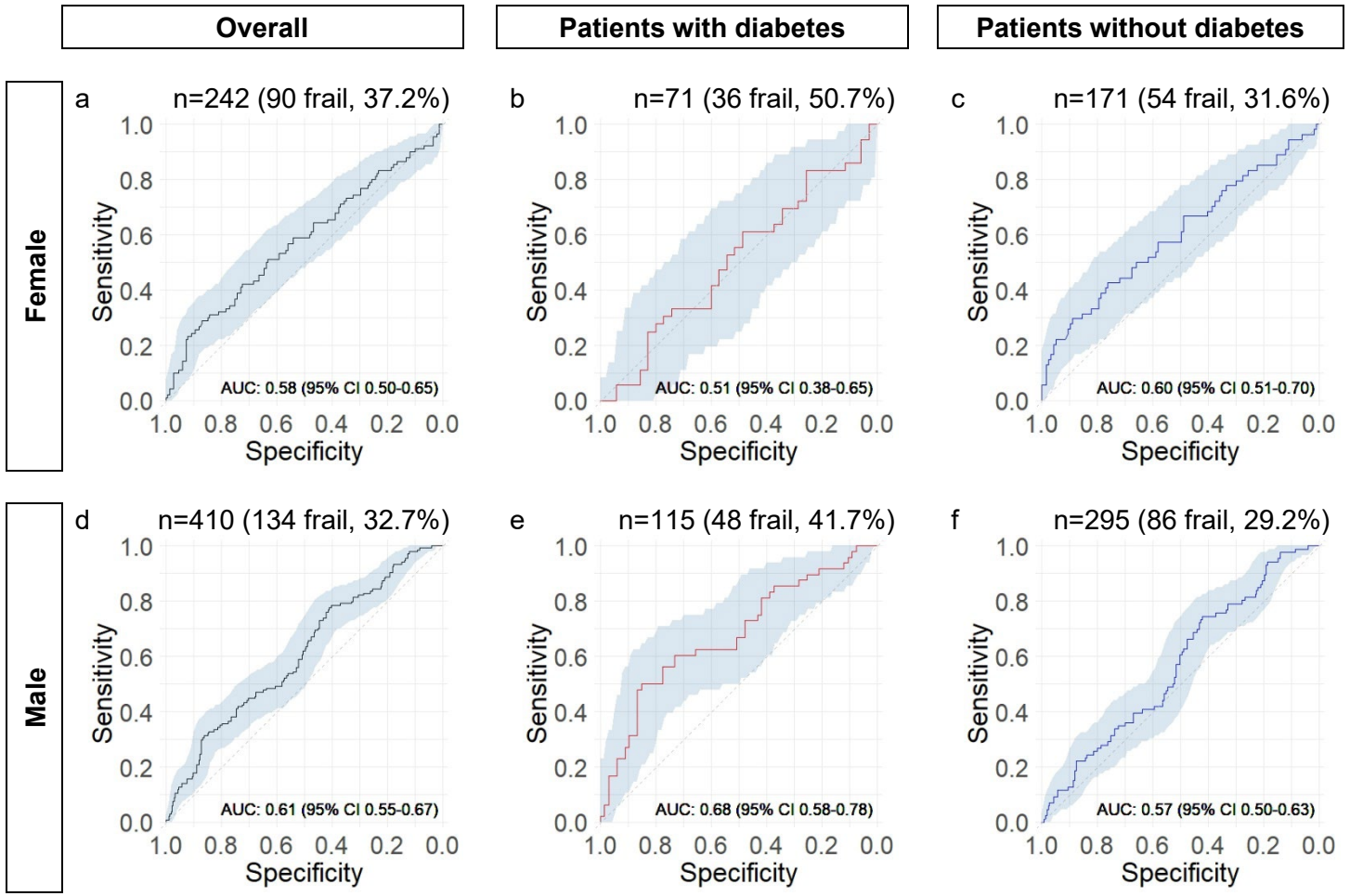
CARE = Cancer and Aging Resilience Evaluation, HU = Hounsfield Units, SMD = skeletal muscle density.

Figure 10. ROC Curve Results for the Classification of Frailty Using SMD, Stratified by Gender and Diabetes (CARE Registry, N = 872)



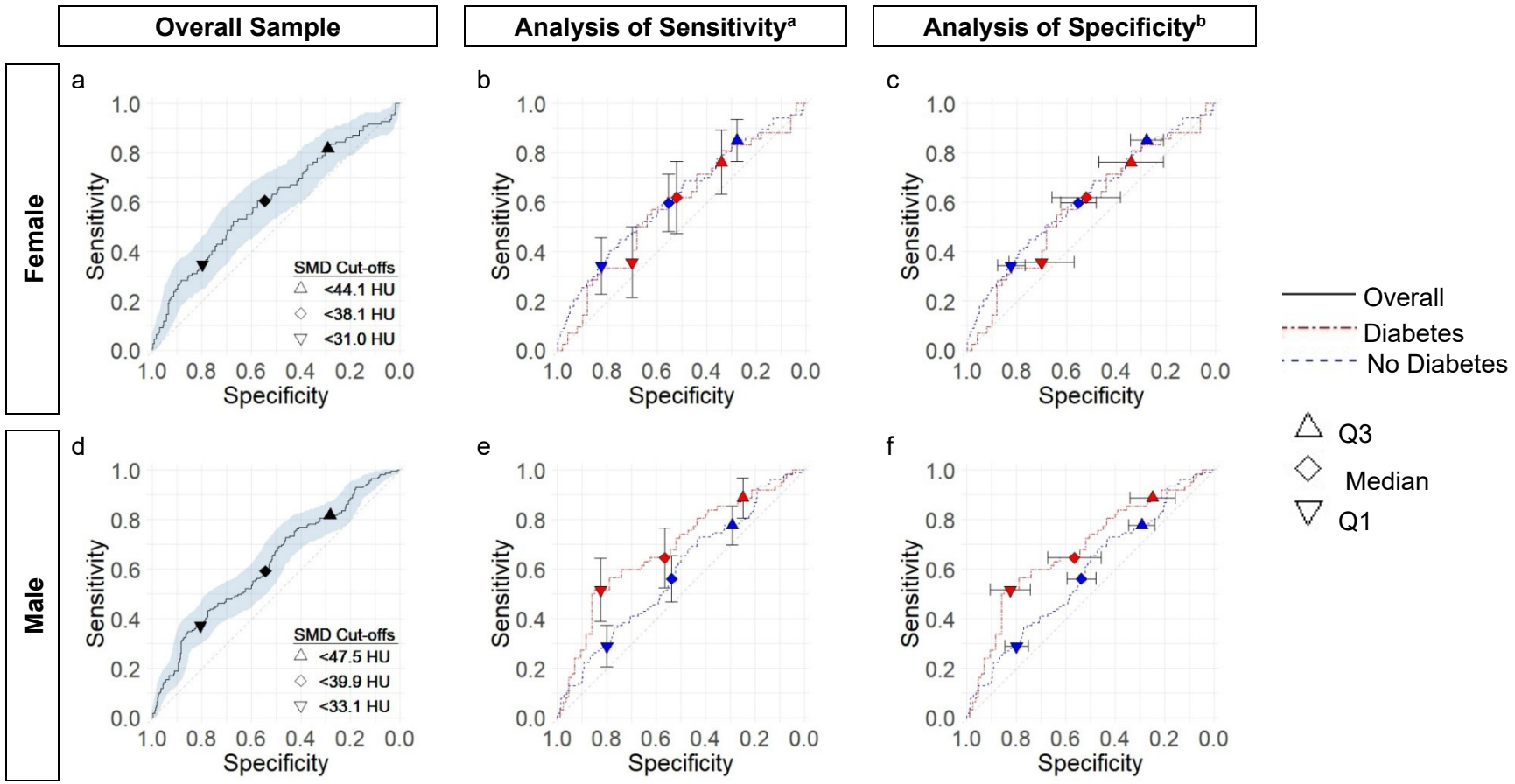
AUC = area under the ROC curve, CARE = Cancer and Aging Resilience Evaluation, HU = Hounsfield Units, ROC = receiver operating characteristic, SMD = skeletal muscle density.

Figure 11. Secondary Analyses—ROC Curve Results for the Classification of Frailty Using SMD, Stratified by Gender and Diabetes (CARE Registry Pre-treatment Sample, N = 652)



AUC = area under the ROC curve, CARE = Cancer and Aging Resilience Evaluation, HU = Hounsfield Units, ROC = receiver operating characteristic, SMD = skeletal muscle density.

Figure 12. Sensitivity and Specificity Results for SMD Quartile Cut-off Points and Assessment of Modification by Diabetes Status (CARE Registry, N = 872)

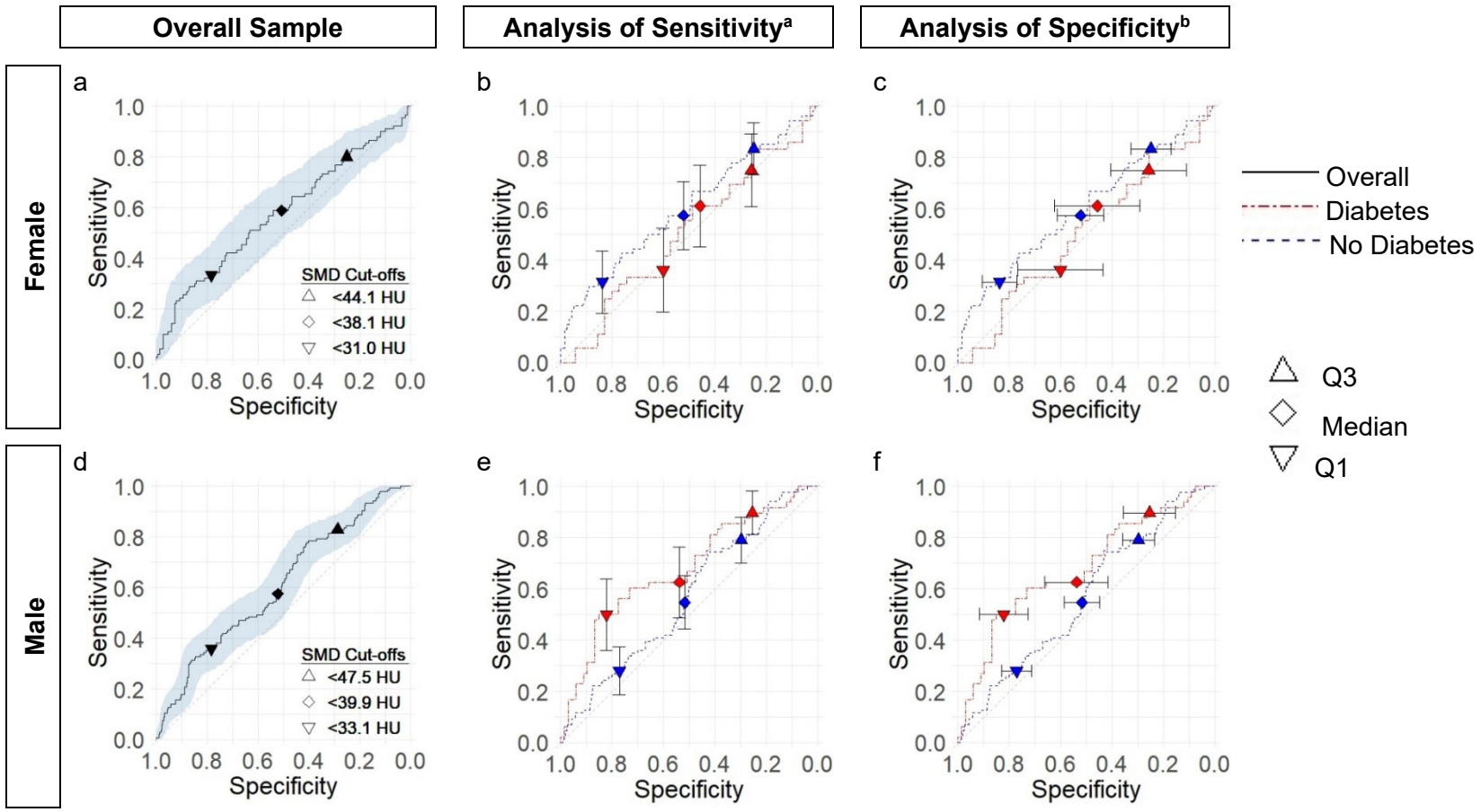


Cancer and Aging Resilience Evaluation, HU = Hounsfield Units, Q1 = 1st quartile, Q3 = 3rd quartile, SMD = skeletal muscle density.

[a]Sensitivity differences (diabetes vs. no diabetes) for Q1, median, and Q3 gender-specific cut-off points: 0.01 HU (-0.17 to 0.20), 0.02 HU (-0.16 to 0.21), -0.09 HU (-0.24 to 0.07) for women; 0.23 HU (0.07 to 0.38), 0.08 HU (-0.07 to 0.24), 0.11 HU (0.00 to 0.22) for men.

[b]Specificity differences for Q1, median, and Q3 gender-specific cut-off points: -0.12 (-0.27 to 0.02), -0.03 (-0.19 to 0.12), 0.06 (-0.08 to 0.21) for women; 0.02 (-0.07 to 0.12), 0.03 (-0.09 to 0.15), -0.04 (-0.15 to 0.06) for men.

Figure 13. Secondary Analyses—Sensitivity and Specificity Results for SMD Quartile Cut-off Points and Assessment of Modification by Diabetes Status (CARE Registry Pre-treatment Sample, N = 652)



CARE = Cancer and Aging Resilience Evaluation, HU = Hounsfield Units, Q1 = 1st quartile, Q3 = 3rd quartile, SMD = skeletal muscle density.

[a]Sensitivity differences (diabetes vs. no diabetes) for Q1, median, and Q3 gender-specific cut-off points: 0.05 (-0.16 to 0.25), 0.04 (-0.17 to 0.24), -0.08 (-0.26 to 0.09) for women; 0.22 (0.05 to 0.39), 0.08 (-0.09 to 0.25), 0.11 (-0.02 to 0.23) for men.

[b]Specificity differences for Q1, median, and Q3 gender-specific cut-off points: -0.24 (-0.42 to -0.06), -0.06 (-0.25 to 0.12), 0.01 (-0.16 to 0.18) for women; 0.05 (-0.06 to 0.16), 0.02 (-0.12 to 0.16), -0.04 (-0.16 to 0.08) for men.

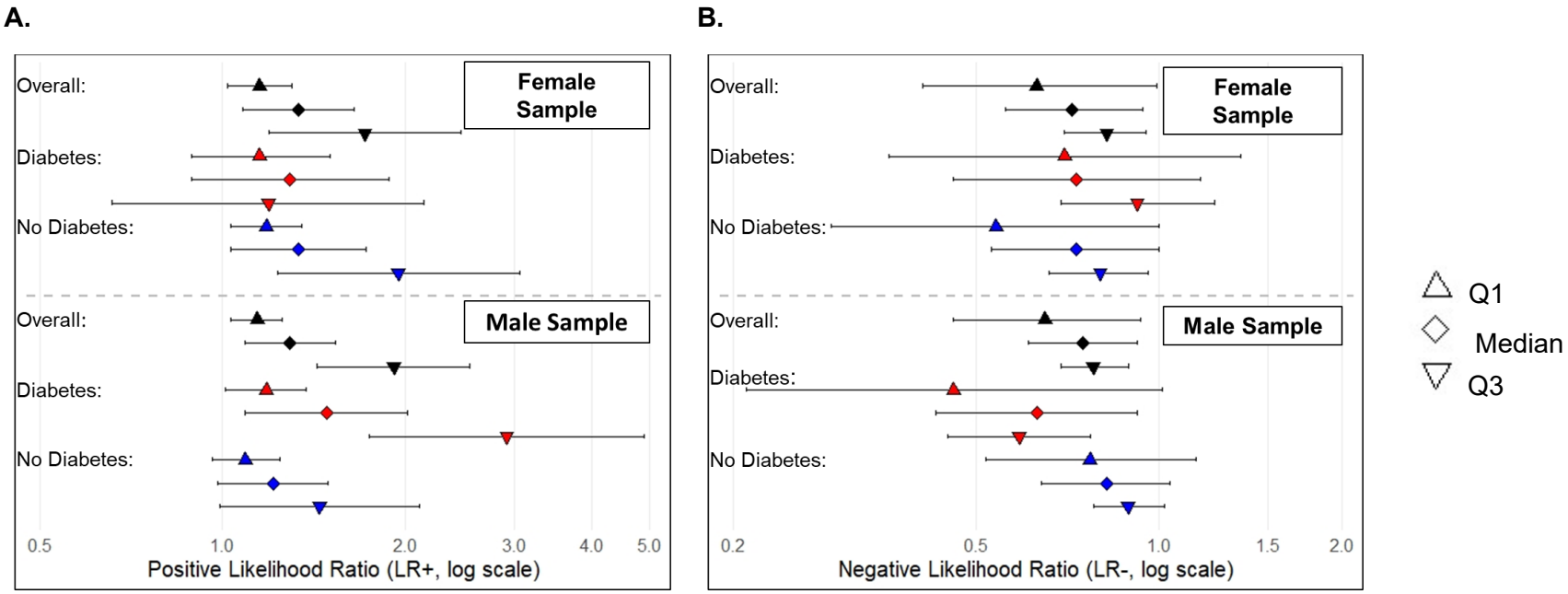
Table 16. Sensitivity, Specificity, Positive Likelihood Ratios, and Negative Likelihood Ratios for SMD Quartile Cut-off Points (CARE Registry, N = 872)

Gender	Stratum	SMD Quartile Cut-off Points[a]	Sensitivity	Specificity	Positive Likelihood Ratio (95% CI)	Negative Likelihood Ratio (95% Ci)
Female	Overall	Q1	0.35	0.80	1.71 (1.19 to 2.46)	0.82 (0.70 to 0.95)
		Median	0.61	0.55	1.33 (1.08 to 1.64)	0.72 (0.56 to 0.94)
		Q3	0.82	0.29	1.15 (1.02 to 1.30)	0.63 (0.41 to 0.99)
	Diabetes	Q1	0.36	0.70	1.19 (0.66 to 2.14)	0.92 (0.69 to 1.23)
		Median	0.62	0.52	1.29 (0.89 to 1.87)	0.73 (0.46 to 1.17)
		Q3	0.76	0.34	1.15 (0.89 to 1.50)	0.70 (0.36 to 1.36)
	No Diabetes	Q1	0.34	0.82	1.94 (1.23 to 3.07))	0.80 (0.66 to 0.96)
		Median	0.60	0.55	1.33 (1.03 to 1.72)	0.73 (0.53 to 1.00)
		Q3	0.85	0.28	1.18 (1.03 to 1.35)	0.54 (0.29 to 1.00)
Male	Overall	Q1	0.37	0.80	1.91 (1.43 to 2.54)	0.78 (0.69 to 0.89)
		Median	0.59	0.54	1.29 (1.09 to 1.53)	0.75 (0.61 to 0.92)
		Q3	0.82	0.28	1.14 (1.03 to 1.25)	0.65 (0.46 to 0.93)
	Diabetes	Q1	0.52	0.82	2.92 (1.74 to 4.91)	0.59 (0.45 to 0.77)
		Median	0.65	0.56	1.48 (1.09 to 2.01)	0.63 (0.43 to 0.92)
		Q3	0.89	0.25	1.18 (1.01 to 1.37)	0.46 (0.21 to 1.01)
	No Diabetes	Q1	0.29	0.80	1.44 (0.99 to 2.10)	0.89 (0.78 to 1.02)
		Median	0.56	0.54	1.21 (0.98 to 1.49)	0.82 (0.64 to 1.04)
		Q3	0.78	0.29	1.09 (0.96 to 1.24)	0.77 (0.52 to 1.15)

CARE = Cancer and Aging Resilience Evaluation, HU = Hounsfield Units, Q1 = 1st quartile, Q3 = 3rd quartile, SMD = skeletal muscle density.

[a]Gender-specific quartile cut-off points were <31.0 HU (Q1), <38.1 HU (median), <44.1 HU (Q3) for women; <33.1 HU (Q1), <39.9 HU (median), <47.5 HU (Q3) for men.

Figure 14. Positive and Negative Likelihood Ratios for SMD Quartile Cut-off Points for the Overall Sample and by Diabetes Status (CARE Registry, N = 872)[a]



CARE = Cancer and Aging Resilience Evaluation, HU = Hounsfield Units, LR+ = positive likelihood ratio, LR- = negative likelihood ratio, Q1 = 1st quartile, Q3 = 3rd quartile, SMD = skeletal muscle density.

[a]Gender-specific quartile cut-off points were <31.0 HU (Q1), <38.1 HU (median), <44.1 HU (Q3) for women; <33.1 HU (Q1), <39.9 HU (median), <47.5 HU (Q3) for men.

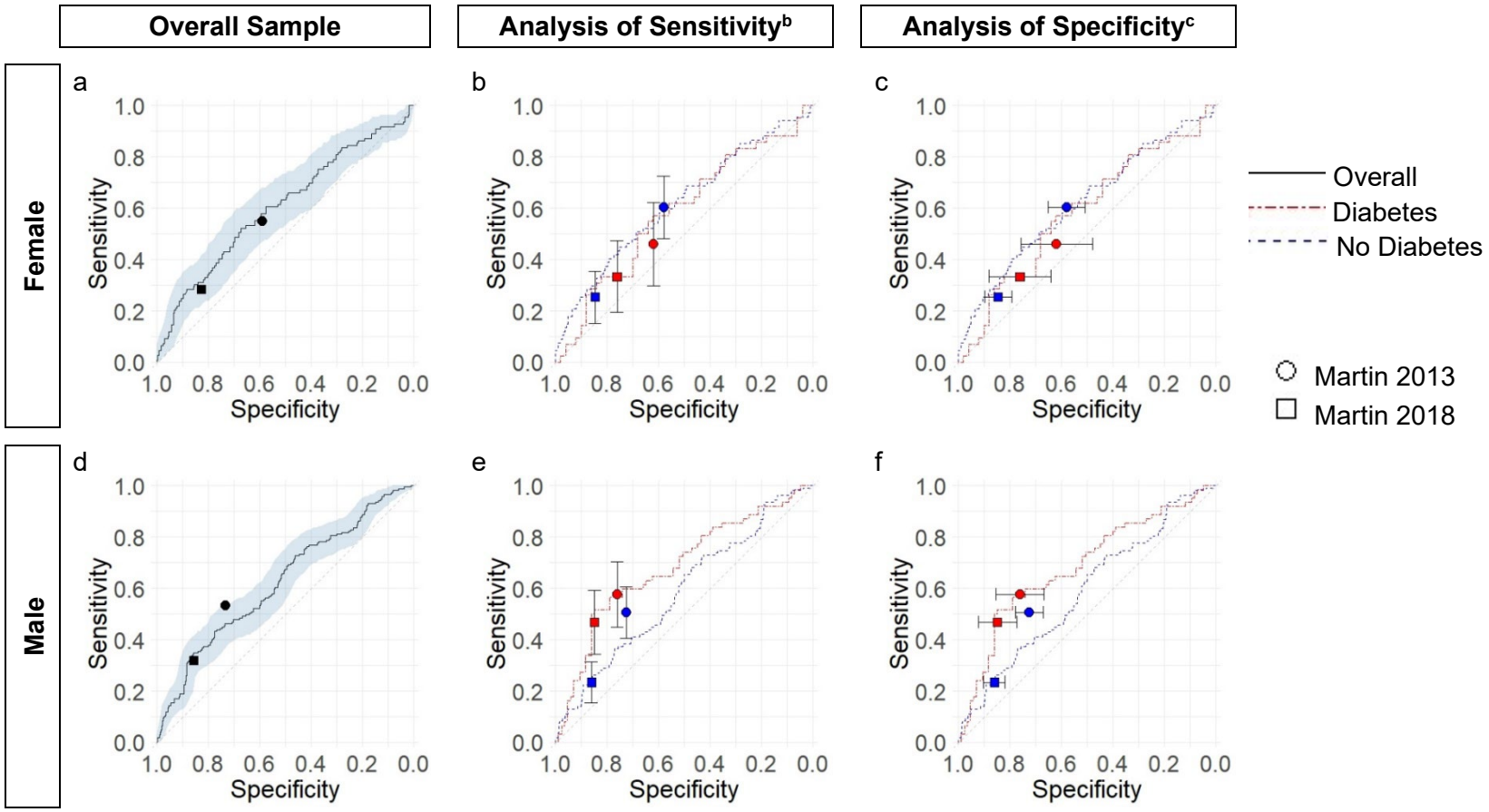
Table 17. Secondary Analyses—Sensitivity, Specificity, Positive Likelihood Ratio, and Negative Likelihood Ratio for SMD Quartile Cut-off Points (CARE Registry Pre-treatment Sample, N = 652)

Gender	Stratum	SMD Quartile Cut-off Points[a]	Sensitivity	Specificity	Positive Likelihood Ratio (95% CI)	Negative Likelihood Ratio (95% Ci)
Female	Overall	Q1	0.33	0.78	1.54 (1.01 to 2.34)	0.85 (0.72 to 1.01)
		Median	0.59	0.51	1.19 (0.94 to 1.51)	0.81 (0.61 to 1.09)
		Q3	0.80	0.25	1.07 (0.93 to 1.22)	0.80 (0.49 to 1.31)
	Diabetes	Q1	0.36	0.60	0.90 (0.50 to 1.64)	1.06 (0.74 to 1.53)
		Median	0.61	0.46	1.13 (0.75 to 1.68)	0.85 (0.49 to 1.47)
		Q3	0.75	0.26	1.01 (0.77 to 1.32)	0.97 (0.44 to 2.16)
	No Diabetes	Q1	0.31	0.84	1.94 (1.10 to 3.43)	0.82 (0.67 to 1.00)
		Median	0.57	0.52	1.20 (0.89 to 1.62)	0.82 (0.57 to 1.17)
		Q3	0.83	0.25	1.11 (0.95 to 1.30)	0.67 (0.34 to 1.32)
Male	Overall	Q1	0.36	0.78	1.65 (1.20 to 2.27)	0.82 (0.71 to 0.94)
		Median	0.57	0.52	1.20 (0.99 to 1.45)	0.82 (0.65 to 1.02)
		Q3	0.83	0.29	1.16 (1.04 to 1.29)	0.60 (0.40 to 0.91)
	Diabetes	Q1	0.50	0.82	2.79 (1.55 to 5.01)	0.61 (0.45 to 0.83)
		Median	0.63	0.54	1.35 (0.96 to 1.90)	0.70 (0.46 to 1.07)
		Q3	0.90	0.25	1.20 (1.01 to 1.42)	0.41 (0.16 to 1.04)
	No Diabetes	Q1	0.28	0.77	1.22 (0.80 to 1.85)	0.94 (0.80 to 1.09)
		Median	0.55	0.52	1.13 (0.89 to 1.44)	0.88 (0.67 to 1.15)
		Q3	0.79	0.30	1.12 (0.98 to 1.29)	0.71 (0.45 to 1.12)

CARE = Cancer and Aging Resilience Evaluation, HU = Hounsfield Units, Q1 = 1st quartile, Q3 = 3rd quartile, SMD = skeletal muscle density.

[a]Gender-specific quartile cut-off points were <31.0 HU (Q1), <38.1 HU (median), <44.1 HU (Q3) for women; <33.1 HU (Q1), <39.9 HU (median), <47.5 HU (Q3) for men.

Figure 15. Secondary Analyses—Sensitivity and Specificity Results for Low-SMD Criteria (Martin *et al*. 2013 and Martin *et al*. 2018) and Assessment of Modification by Diabetes Status (CARE Registry, N = 872)[a]



BMI = body mass index, CARE = Cancer and Aging Resilience Evaluation, CI = confidence interval, HU = Hounsfield units, SMD = skeletal muscle density.

[a]Estimates for Martin *et al*. 2013 criteria were calculated for patients with known BMI.

[b]Sensitivity differences (diabetes vs. no diabetes) for low SMD based on Martin *et al*. 2013 criteria and Martin *et al*. 2018 criteria: -0.14 HU (-0.35 to 0.06) and 0.08 HU (-0.09 to 0.25) for women; 0.07 HU (-0.09 to 0.23) and 0.23 HU (0.09 to 0.38) for men.

[c]Specificity differences (diabetes vs. no diabetes) for low SMD based on Martin *et al*. 2013 criteria and Martin *et al*. 2018 criteria: 0.04 HU (-0.12 to 0.20) and -0.09 HU (-0.22 to 0.05) for women; 0.04 HU (-0.07 to 0.14) and -0.01 HU (-0.10 to 0.07) for men.

Table 18. Secondary Analyses—Sensitivity, Specificity, Positive Likelihood Ratio, and Negative Likelihood Ratio for Low-SMD Criteria (Martin *et al***.** 2013 and Martin *et al***.** 2018, CARE Registry Sample, N = 872)

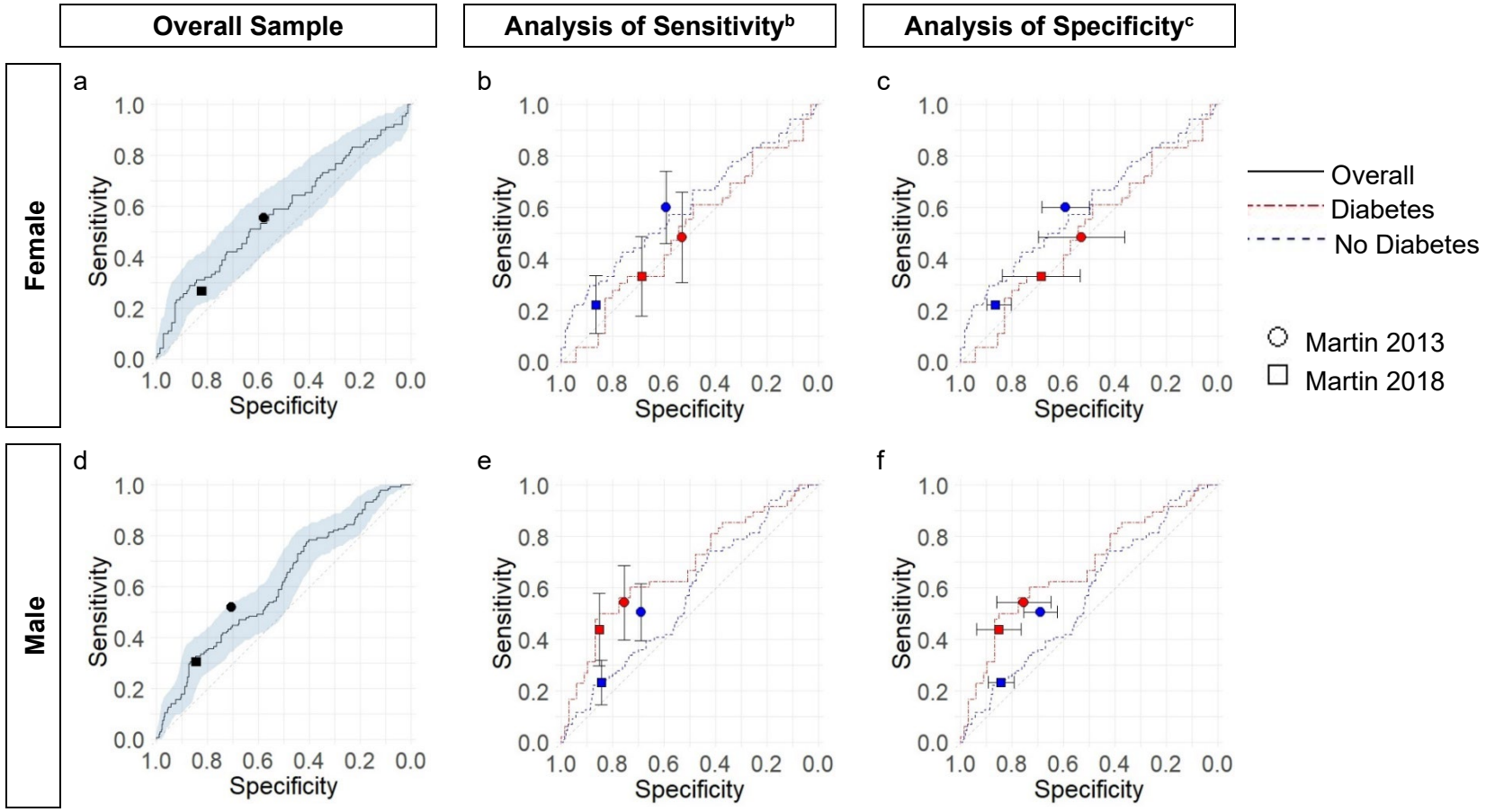
Gender	Stratum	Low SMD Criteria[a]	Sensitivity	Specificity	Positive Likelihood Ratio (95% CI)	Negative Likelihood Ratio (95% Ci)
Female	Overall	Martin 2013	0.55	0.59	1.33 (1.05 to 1.69)	0.77 (0.60 to 0.98)
		Martin 2018	0.28	0.83	1.64 (1.09 to 2.47)	0.87 (0.76 to 0.99)
	Diabetes	Martin 2013	0.46	0.62	1.20 (0.72 to 1.99)	0.88 (0.60 to 1.27)
		Martin 2018	0.33	0.76	1.39 (0.72 to 2.67)	0.88 (0.67 to 1.14)
	No Diabetes	Martin 2013	0.60	0.58	1.43 (1.10 to 1.87)	0.69 (0.49 to 0.95)
		Martin 2018	0.25	0.85	1.64 (0.96 to 2.80)	0.88 (0.76 to 1.03)
Male	Overall	Martin 2013	0.53	0.73	1.99 (1.58 to 2.49)	0.64 (0.54 to 0.76)
		Martin 2018	0.32	0.86	2.23 (1.60 to 3.12)	0.79 (0.71 to 0.89)
	Diabetes	Martin 2013	0.58	0.76	2.39 (1.54 to 3.71)	0.56 (0.40 to 0.77)
		Martin 2018	0.47	0.85	3.06 (1.74 to 5.39)	0.63 (0.49 to 0.81)
	No Diabetes	Martin 2013	0.51	0.72	1.83 (1.39 to 2.41)	0.68 (0.55 to 0.85)
		Martin 2018	0.23	0.86	1.67 (1.06 to 2.61)	0.89 (0.79 to 1.00)

CARE = Cancer and Aging Resilience Evaluation, BMI = body mass index, CI = confidence interval, SMD = skeletal muscle density.

[a]Low-SMD cut-points were determined based on associations with survival and hospital length of stay in Martin *et al*. 2013 and Martin *et al*. 2018, respectively. Estimates for Martin *et al.* 2013 criteria were calculated for patients with known BMI.

References: Martin, L., et al., Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. Journal of clinical oncology, 2013. 31(12): p. 1539-1547; Martin, L., et al., Assessment of computed tomography (CT)-defined muscle and adipose tissue features in relation to short-term outcomes after elective surgery for colorectal cancer: a multicenter approach. Annals of surgical oncology, 2018. 25(9): p. 2669-2680.

Figure 16. Secondary Analyses—Sensitivity and Specificity Results for Low-SMD Criteria (Martin *et al***.** 2013 and Martin *et al***.** 2018) and Assessment of Modification by Diabetes Status (CARE Registry Pre-treatment Sample, N = 652)[a]



BMI = body mass index, CARE = Cancer and Aging Resilience Evaluation, CI = confidence interval, HU = Hounsfield Units, SMD = skeletal muscle density.

[a]Estimates for Martin *et al*. 2013 criteria were calculated for patients with known BMI.

[b]Sensitivity differences (diabetes vs. no diabetes) for low SMD based on Martin *et al*. 2013 criteria and Martin *et al*. 2018 criteria: -0.12 HU (CI, -0.34 to 0.11) and 0.11 HU (-0.08 to 0.30) for women; 0.04 HU (-0.15 to 0.22) and 0.20 HU (0.04 to 0.37) for men.

[c]Specificity differences (diabetes vs. no diabetes) for low SMD based on Martin *et al*. l 2013 criteria and Martin *et al*. 2018 criteria: -0.06 HU (CI, -0.25 to 0.13) and -0.18 HU (-0.34 to -0.01) for women; 0.07 HU (-0.06 to 0.19) and 0.01 HU (-0.09 to 0.11) for men.

Table 19. Secondary Analyses—Sensitivity, Specificity, Positive Likelihood Ratio, and Negative Likelihood Ratio for Low-SMD Criteria (Martin *et al.* 2013 and Martin *et al.* 2018; CARE registry Pre-treatment Sample, N = 652)

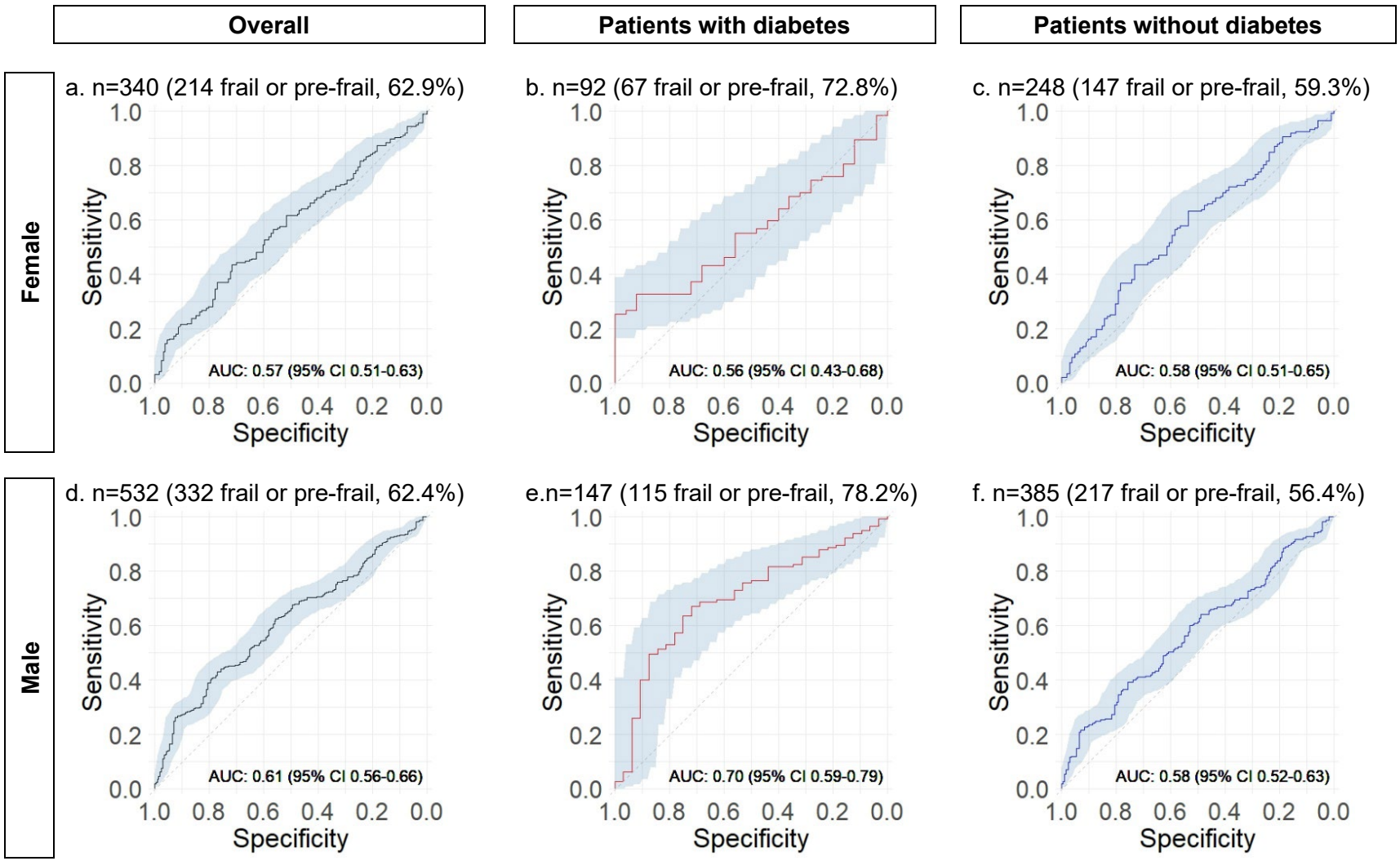
Gender	Stratum	Low SMD Criteria[a]	Sensitivity	Specificity	Positive Likelihood Ratio (95% CI)	Negative Likelihood Ratio (95% Ci)
Female	Overall	Martin 2013	0.56	0.58	1.31 (1.00 to 1.72)	0.77 (0.58 to 1.02)
		Martin 2018	0.27	0.82	1.50 (0.93 to 2.44)	0.89 (0.77 to 1.03)
	Diabetes	Martin 2013	0.48	0.53	1.03 (0.62 to 1.71)	0.97 (0.61 to 1.55)
		Martin 2018	0.33	0.69	1.06 (0.54 to 2.08)	0.97 (0.70 to 1.34)
	No Diabetes	Martin 2013	0.60	0.59	1.47 (1.07 to 2.02)	0.68 (0.47 to 0.98)
		Martin 2018	0.22	0.86	1.63 (0.83 to 3.19)	0.90 (0.77 to 1.06)
Male	Overall	Martin 2013	0.52	0.70	1.76 (1.37 to 2.26)	0.68 (0.56 to 0.83)
		Martin 2018	0.31	0.84	1.96 (1.35 to 2.86)	0.82 (0.73 to 0.93)
	Diabetes	Martin 2013	0.54	0.75	2.21 (1.34 to 3.64)	0.61 (0.43 to 0.85)
		Martin 2018	0.44	0.85	2.93 (1.52 to 5.65)	0.66 (0.51 to 0.87)
	No Diabetes	Martin 2013	0.51	0.69	1.63 (1.20 to 2.19)	0.72 (0.56 to 0.91)
		Martin 2018	0.23	0.84	1.47 (0.90 to 2.42)	0.91 (0.80 to 1.04)

CARE = Cancer and Aging Resilience Evaluation, BMI = body mass index, CI = confidence interval, SMD = skeletal muscle density.

[a]Low-SMD cut-points were determined based on associations with survival and hospital length of stay in Martin *et al*. 2013 and Martin *et al*. 2018, respectively. Estimates for Martin *et al*. 2013 criteria were calculated for patients with known BMI.

References: Martin, L., et al., Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. Journal of clinical oncology, 2013. 31(12): p. 1539-1547; Martin, L., et al., Assessment of computed tomography (CT)-defined muscle and adipose tissue features in relation to short-term outcomes after elective surgery for colorectal cancer: a multicenter approach. Annals of surgical oncology, 2018. 25(9): p. 2669-2680.

Figure 17. Sensitivity Analysis—ROC Curve Results for the Classification of Frail or Pre-frail Status Using SMD, Stratified by Gender and Diabetes (CARE Registry, N = 872)



AUC = area under the ROC curve, CARE = Cancer and Aging Resilience Evaluation, HU = Hounsfield Units, ROC = receiver operating characteristic, SMD = skeletal muscle density.

Table 20. Sensitivity Analysis—Sensitivity, Specificity, Positive Likelihood Ratio, and Negative Likelihood Ratio for SMD Quartile Cut-off Points in Classifying Frail or Pre-frail Status (CARE Registry, N = 872)

			Main Analysis[a]		Sensitivity Analysis[b]			
Gender	Stratum	SMD Quartile Cut-off Points[c]	Sensitivity	Specificity	Sensitivity	Specificity	Positive Likelihood Ratio (95% CI)	Negative Likelihood Ratio (95% Ci)
Female	Overall	Q1	0.35	0.80	0.28	0.80	1.41 (0.94 to 2.13)	0.90 (0.80 to 1.01)
		Median	0.61	0.55	0.55	0.57	1.28 (1.01 to 1.61)	0.79 (0.64 to 0.98)
		Q3	0.82	0.29	0.75	0.27	1.03 (0.90 to 1.17)	0.92 (0.63 to 1.33)
	Diabetes	Q1	0.36	0.70	0.34	0.72	1.23 (0.60 to 2.49)	0.91 (0.68 to 1.23)
		Median	0.62	0.52	0.55	0.48	1.06 (0.69 to 1.64)	0.93 (0.57 to 1.52)
		Q3	0.76	0.34	0.70	0.28	0.97 (0.73 to 1.30)	1.07 (0.51 to 2.21)
	No Diabetes	Q1	0.34	0.82	0.25	0.82	1.41 (0.85 to 2.34)	0.91 (0.80 to 1.04)
		Median	0.60	0.55	0.54	0.59	1.34 (1.01 to 1.77)	0.77 (0.60 to 0.97)
		Q3	0.85	0.28	0.78	0.27	1.06 (0.91 to 1.23)	0.84 (0.54 to 1.31)
Male	Overall	Q1	0.37	0.80	0.30	0.83	1.77 (1.25 to 2.51)	0.84 (0.77 to 0.93)
		Median	0.59	0.54	0.55	0.59	1.35 (1.12 to 1.64)	0.76 (0.64 to 0.89)
		Q3	0.82	0.28	0.77	0.29	1.09 (0.98 to 1.21)	0.78 (0.58 to 1.05)
	Diabetes	Q1	0.52	0.82	0.38	0.91	4.08 (1.36 to 12.28)	0.68 (0.57 to 0.82)
		Median	0.65	0.56	0.60	0.75	2.40 (1.29 to 4.45)	0.53 (0.40 to 0.72)
		Q3	0.89	0.25	0.84	0.31	1.23 (0.96 to 1.57)	0.50 (0.26 to 0.98)
	No Diabetes	Q1	0.29	0.80	0.26	0.82	1.40 (0.95 to 2.07)	0.91 (0.82 to 1.01)
		Median	0.56	0.54	0.53	0.56	1.20 (0.97 to 1.49)	0.84 (0.69 to 1.02)
		Q3	0.78	0.29	0.74	0.29	1.03 (0.91 to 1.17)	0.92 (0.66 to 1.27)

CARE = Cancer and Aging Resilience Evaluation, HU = Hounsfield Units, Q1 = 1st quartile, Q3 = 3rd quartile, SMD = skeletal muscle density.

[a]Main analyses assessed the classification for frail status vs. pre-frail or robust.

[b]Sensitivity analyses assessed the classification of frail or pre-frail status vs. robust.

[c]Gender-specific quartile cut-off points were <31.0 HU (Q1), <38.1 HU (median), <44.1 HU (Q3) for women; <33.1 HU (Q1), <39.9 HU (median), <47.5 HU (Q3) for men.

CHAPTER 5: GERIATRIC ASSESSMENT IMPAIRMENT PROFILES IN OLDER ADULTS WITH GASTROINTESTINAL CANCERS: LATENT CLASS ANALYSIS OF THE CARE REGISTRY

5.1. Introduction

Cancer is broadly considered a disease of aging, and in the US, half of new cancer diagnoses occur among adults age 65 or older.[1] Both younger and older adults with cancer may benefit from treatment with chemotherapy, and age alone is not a contraindication to therapy.[142,143] However, older adults with cancer often have health deficits and impairments that do not occur in isolation. Based on a systematic review of observational studies using multi-disciplinary clinical assessments, 43-64% of older adults with cancer are estimated to have two or more health deficits.[2] For patients with gastrointestinal cancers, one US registry study has even reported a high prevalence (>60%) of two or more impairments among adults ages 60-64.[3] Thus, the presence of multiple geriatric impairments is common for older adults with cancer, and because of individual differences in how comorbid conditions, disabilities, and health deficits accrue over the adult lifespan, older adults with cancer are a heterogenous population with variable treatment tolerability. Understanding patterns of impairments for older adults and how they may interact is critical for developing interventions to support treatment completion and patient care.

In acknowledging these challenges in treating older adults, the American Society of Clinical Oncology (ASCO) recommends using a clinical tool called geriatric assessment to identify vulnerabilities or geriatric impairments that are not regularly captured in oncology assessments.[5] Geriatric assessments can be used to evaluate multiple health domains such as physical function, falls, depression, cognition, nutrition, and comorbidity.[5] Geriatric assessment

can also be used to identify frailty, a geriatric syndrome that is described as a state of increased vulnerability due to accrued impairments in multiple body systems, and a diminished ability to respond to even mild stresses (e.g., treatment, illness, injury).[20,21] Clinical trials have demonstrated the efficacy of geriatric assessment in reducing grade 3 or higher chemotherapy-related toxic effects with one study at the City of Hope National Medical Center reporting a 10-percentage point reduction from 61% in patients receiving standard of care to 51% in patients receiving geriatric assessment-driven intervention[144,145] Successful delivery of these trial interventions notably required review and input from a multidisciplinary team including a geriatric oncologist, nurse practitioner, social worker, physical/occupation therapist, nutritionist, and pharmacist. Thus, successful real-world intervention on geriatric impairments requires knowledge of multiple impairments and coordination between health services staff. Identifying impairment patterns from the multiple health domains assessed in a routine geriatric assessment can facilitate intervention planning and the packaging of support services.

One previous study has used a data-driven, exploratory, statistical clustering method to identify health profiles based on combinations of geriatric assessment findings. Four health profiles were identified (relatively healthy, malnourished, cognitive and/or mood impaired, and globally impaired), and impaired health profiles were found to be associated with unscheduled hospital admissions and 1-year mortality.[58] However, the analyses were conducted in a sample that included multiple cancers which may be too heterogenous to identify impairment patterns for patients with specific cancer types, such as gastrointestinal cancer. Colorectal and other gastrointestinal cancers are among the most common cancers for older men and women globally, and treatment involves multiple modalities (e.g., major surgery and chemotherapy) which may be significant stressors to older adult patients.[146]

Our study objective was to identify and describe distinct geriatric assessment impairment classes using latent class analysis (LCA) in older patients with gastrointestinal malignancies.

We characterized these classes and assessed 1-year survivorship and mortality based on class membership.

5.2. Methods

5.2.1. Study Sample

We included patients with gastrointestinal malignancies (stages I-IV) who completed the CARE tool and consented to enroll in the CARE Registry (see **Figure 17** for inclusion flowchart). The CARE tool is a self-reported geriatric assessment that was adapted from the Cancer and Aging Research Group (CARG) geriatric assessment developed by Hurria and colleagues.[45] All analyses were conducted among the older patient sample with complete information on impairment domains, patients with at least one reported impairment, and patients who completed the CARE tool with no prior chemotherapy in the past 6 months and before starting current chemotherapy ("pre-chemotherapy sample").

5.2.2. Indicators Used to Determine Impairment Profiles

We conducted LCA using 13 geriatric assessment impairments defined in the CARE tool as latent class indicators (see **Table 11**).[3] Indicators were dichotomized based on the presence or absence of the impairment. The impairments included recent falls (≥1 falls in the past 6 months); walking (significant limitations in walking one block); instrumental activities of daily living (IADL, ≥ 2 impairments); activities of daily living (ADL, any ADL impairment); weight loss (≥3% loss within 1 month or ≥6% loss within 6 months); low activity (Eastern Cooperative Oncology Group Performance Status, ECOG-PS ≥3); social activity interference (reported "most" or "all of the time"); multimorbidity (≥4 comorbidities reported on the Older Americans and Services, OARS, comorbidity measure[131,132,147]; low social support (i.e., someone to help at most "some of the time" on the Medical Outcomes Study Social Support Survey, MOS-SSS[148]); anxiety (Patient-Reported Outcomes Measurement Information System, PROMIS®, Anxiety T-

score >60); depression (PROMIS Depression T-score >60); cognitive impairment (PROMIS Cognitive Function T-score <40); or polypharmacy (≥9 daily medications).

5.2.3. Outcomes

Vital status and date of death was identified up to October 2021 using linkage with LexisNexis® and patient name and social security number. Zip code and date of diagnosis were used for confirmation. We reported deaths that occurred within 1 year after CARE tool completion.

5.2.4. Patient Characteristics

Frailty score was calculated based on the principles of deficit accumulation using 44 health deficit items in the CARE tool, and scores were only calculated for patients who responded to ≥24 items.[7-9,112-114] Items were coded as indicating the presence of deficit ('1'), absence of the deficit ('0'), or intermediate responses(e.g., 'sometimes' or 'maybe'; '0.5'), and patient frailty scores were assigned to represent the overall proportion of deficits (range 0-1). Frailty scores were categorized using previously defined thresholds for frailty indices: robust (0-0.2), pre-frail (0.2-0.35), or frail (>0.35).[115]

The following demographics were reported in the CARE tool: race (White, Black or African American, Native American or Alaskan, Asian, Native Hawaiian, other), ethnicity (Hispanic or Latino, non-Hispanic), education level (less than high school, high school graduate, associate/Bachelors, advanced degree), and marital status (single, widowed/divorced, married). The self-reported race and ethnicity variables were taken to represent social constructs and reflected racial self-classification—one dimension of race characterized by closed-ended, self-identification questions that fit a racial schema for data collection.[134] Additional information from electronic health records was extracted by a trained research assistant and included age, gender, height and weight (measured ≤2 weeks before treatment start date) for calculation of

BMI, cancer type and stage, and current chemotherapy treatment line. Age was self-reported as an integer in the health records and represented chronologic age. Gender (male or female) was self-reported by patients upon registration with UAB Medicine and represented self-identified sexual identity. For data cleaning purposes, patients reporting current weight <50 pounds were excluded. Patient BMI was categorized (underweight, normal, overweight, or obese), and we incorporated Asian- (≥22.2 and ≥26.9 kg/m^2) and Black-specific (≥23.4 and ≥28.1 kg/m^2) cut-off points for overweight and obese based on prior work.[135] High-risk malignancies (pancreatic, hepatobiliary, and esophageal cancers), and low-risk malignancies (colorectal, gastrointestinal stromal tumors [GIST], neuroendocrine tumors, and other) were categorized based on typical estimated survival and 1-year mortality.[116]

5.2.5. Statistical Analysis

LCA is a statistical procedure that is used to detect heterogeneity in a population sample and to identify qualitatively different subgroups.[123] As a form of person-centered mixture modeling, LCA uses study participant responses and categorical indicator variables to identify latent (or unobserved) groups that share patterns of responses to observed variables.[124] The underlying assumption in LCA is that membership in latent classes is antecedent and can explain patterns of survey responses, categorial indicator variables, or scales.[124,125] We assume that responses on each indicator are conditionally independent of each other given latent class membership.[123] It uses cross-classification of responses on indicator variables to identify each unique response combination that exists within a dataset or population.[123] Then latent class models with 1, 2, 3… etc. resultant classes are fit to the data and posterior probabilities for each class are estimated for respondents.

In the pre-chemotherapy sample of patients with at least one impairment (n=464, Figure 18), we conducted LCA using the 13 impairment indicators to model latent class probabilities. The number of latent classes used to fit the data was determined by evaluating model iterations

containing 1 to 8 classes. Models were evaluated quantitatively and qualitatively using the following criteria: 1.) lower values for Akaike information criteria (AIC), Bayesian information criteria (BIC), and adjusted Bayesian information criterion (aBIC); 2.) bootstrapped likelihood ratio tests (LRT, BLRT, 1,000 replicates); 3.) entropy; 4.) based on substantive interpretation of classes and clinical input.[126] Bootstrap LRT tests the null hypothesis that modeling *k* classes is adequate compared to modeling *k + 1* classes. We evaluated bootstrapped LRT p-values using a 0.05 significance level with significant results indicating that the larger model with *k + 1* classes fit the sample better than the smaller model. Entropy assessed discrimination and values of 0.8 or higher indicate acceptable class separation.[125] Using each patient's posterior probabilities for the *k* classes, we assigned patients to one latent class based on maximum posterior class membership probability.

To facilitate interpretation and labeling of each class, we assessed geriatric assessment impairment probabilities for each latent class and incorporated clinical input. For the resulting latent classes and for the overall patient sample, we reported patient characteristics using counts and percentages for categorical characteristics and using median, first quartile and third quartile for continuous characteristics.

For patients enrolled in the registry before the LexisNexis® linkage in October 2021, we evaluated 1-year mortality risk for each class and presented Kaplan-Meier curves. For comparison, we also estimated 1-year mortality for patients stratified by frailty status. We additionally compared risk between classes using risk differences, risk ratios, and 95% confidence intervals for the contrasts. The latent class with the largest sample size was selected to be the referent class. Risk contrasts and 95% confidence intervals for the contrasts were also provided for the frailty categorizations using patients considered robust as the reference group. Further, in exploratory analyses, we calculated stratified 1-year mortality risks for each latent class to describe estimates in different patient subgroups. Risk estimates were calculated based

on cancer type (high-risk vs. low-risk) and cancer stage (IV vs. I-III) and risk differences and 95% confidence intervals were calculated for each latent class.

As a sensitivity analysis, we conducted single-value imputation to include patients with missing impairment items; missing impairment indicators were recoded to “no impairment” under the temporary assumption that skipped questions were due to no impairment. After imputation, the pre-chemotherapy sample included 600 patients with at least one geriatric assessment impairment and was used in the latent class model identified in primary analyses. A total of 579 patients completed the CARE tool before the latest linkage with LexisNexis® and had available 1-year mortality outcomes; 570 of these patients had calculated frailty scores for comparison. Given the descriptive intent of this work, we did not assess adjusted risk contrasts and did not explore risk factors that should be included in an adjustment set. Analyses were conducted using PROC LCA and PROC LIFETEST in SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC) and Kaplan-Meier curves were generated using the survminer package (ggsurvplot) in R statistical software version 4.1.1. (Comprehensive R Archive Network, CRAN).

5.3. Results

5.3.1. Overall Study Sample

The analytic sample included 464 patients that were predominately white/Caucasian with median age 69 years, and 43% women (**Table 21)**. The sample was closely split between high-risk and low-risk cancer types, 42% of the sample had stage IV disease, and the majority of the sample (74%) was planning to receive their first chemotherapy treatment. While all of the included patients in the sample had at least one impairment; 57% of the sample reported 1-3 impairments (**Figure 17)**. Based on frailty scores, 30% of the sample was considered to be robust (n=137); the remaining sample was evenly split between patients considered pre-frail (n=163, 35%) and patients with frailty (n=164, 35%).

5.3.2. Latent Class Analysis – Model Fit and Class Identification

The LCA model fit criteria indicated 6 distinct classes fit the CARE sample best (**Table 22**). ABIC was lowest for these results. Bootstrapped LRT p-values for models with 1 to 5 latent classes were less than 0.05 indicating that larger models were preferred; a BLRT p-value greater than 0.05 indicated that 6 classes fit the data adequately relative to larger models. After assigning patients to individual classes, posterior probabilities for the resultant 6 classes were ≥80% (see **Table 23**). The 6 impairment latent classes (LC) were labeled based on their impairment probability profiles (**Figure 19**):

LC 1: Mild impairment, n =130 (28%). Characterized by low probabilities (<30%) for functional impairments (i.e., falls, walking, IADLs, ECOG-PS), anxiety, depression, cognition, and social support; multimorbidity and polypharmacy probabilities were >60% and nearly >40%, respectively.

LC 2: Social support impairment, n=56 (12%). Characterized by social support impairment (100%) with 45% probability of weight loss, and low (<5%) probability for functional impairments, multimorbidity, anxiety or depression.

LC 3: Weight loss alone, n = 72 (16%) Characterized by weight loss (100%) with low probabilities (<20%) for other impairments (i.e., multimorbidity, anxiety).

LC 4: Moderate impairment with low anxiety/depression, n=105 (23%), hereafter referred to as "**impaired, low anxiety/depression**" class. Characterized by higher probabilities for functional impairments (walking, IADLs, ADLs), weight loss, physical and social activity impairments compared to the mild impairment class, and low probabilities for anxiety (<15%) and depression (0%).

LC 5: Moderate impairment with anxiety/depression, n = 51 (11%), hereafter referred to as "**impaired with anxiety/depression**" class. Characterized by higher impairment probabilities than the mild impairment class for functional domains (i.e., walking,

IADL, ADL, ECOG-PS), weight loss, social activity, social support, cognition, and high probabilities (>85%) for anxiety and depression.

LC 6: Global impairment, n=50 (11%). Characterized by higher impairment probabilities than moderate impairment classes (LC4, LC5) for functional domains including >90% probability of walking impairments and on ECOG-PS, and 100% probability of IADL and ADL impairment. Probability of social activity impairment and multimorbidity were also greater than the impaired with anxiety/depression class, but probabilities for anxiety and depression were <50%.

5.3.3. Characteristics by Latent Class

The impairment classes had median ages that ranged from 68 to 71 years with similar interquartile ranges (**Table 21**). The social support impairment class and global impairment class had lower percentages of women compared to other classes. The percentage of patients in non-white / non-Caucasian categories was greater in the two impaired latent classes and the global impairment class, and percentages were lower for the mild impairment, social support impairment, and weight loss alone classes. Patients belonging to the social support impairment and impaired with anxiety/depression classes had greater percentages of patients who were widowed, divorced, or separated. The percentage of patients with high-risk cancers and stage IV cancers was >40% (range: 42 to 60%) and >30% (range: 32 to 54%), respectively, for all classes besides the social support impairment class. The impaired with anxiety/depression class and the global impairment class had greater percentages of patients who were planning to receive their 2nd chemotherapy treatment or beyond. More than 50% of patients in each class were overweight or obese except for the impaired with anxiety/depression class, which had the greatest percentage of patients considered normal weight. Additionally, the global impairment class had the largest percentage of patients considered underweight.

For frailty distributions, the mild impairment class had more than half of patients considered pre-frail and 20% of patients were considered frail. The social support impairment class was predominately composed of patients who were robust with no patients considered frail, and the weight loss alone class also had more than half of patients considered robust and only 1 patient considered frail. For the moderate impairment classes (impaired, low anxiety/depression; and impaired with anxiety/depression), more than 90% of patients were pre-frail or frail with slightly higher percentages of frailty for the impaired with anxiety/depression class. The global impairment class was composed entirely of patients with frailty. Self-reported comorbidity distributions are also listed in **Table 21**. Similar to frailty distributions, the social support impairment class and weight loss alone class generally had lower percentages of patients reporting each comorbidity compared to the other impairment classes. The global impairment class had the highest percentage of patients reporting stroke across the 6 latent classes (18% vs. 2-8% other classes).

5.3.4. One-year Mortality by Latent Classes

For 1-year mortality analyses, we excluded 19 patients who were enrolled in the CARE registry after the latest LexisNexis® linkage: n=7 from the mild impairment class; n=2 from the social support impairment class; n=3 from the weight loss alone class; n=3 from the impaired, low anxiety/depression class; n=1 from the impaired with anxiety/depression class; n=3 from the global impairment class. Kaplan-Meier curves for 1-year survival are presented in **Figure 18** based on latent class membership in Panel A and based on frailty categories in Panel B.

One-year mortality risk estimates for latent classes were as follows: mild impairment = 14% (95% CI, 9 to 23%); social support impairment = 22% (12 to 37%); weight loss alone class = 29% (19 to 43%); impaired, low anxiety/depression = 34% (25 to 45%); impaired with anxiety/depression = 50% (35 to 66%); global impairment class = 50% (37 to 66%, **Table 24**). For comparison, 1-year mortality risk estimates for the patient sample based on frailty

classification were as follows: robust = 18% (12 to 27%), pre-frail = 29% (22 to 38%), frail = 40% (32 to 8%). Compared to 1-year mortality with the frailty categories, the latent impairment classes had a greater spread of mortality results, and two classes (impaired with anxiety/depression and global impairment) had risk estimates that was greater than the estimate for the frail categorization.

Based on 1-year mortality risk difference estimates using the mild impairment class as a reference, mortality point estimates were greater for patients assigned to the other impairment classes, although confidence intervals were wide due to class sizes: social support impairment risk difference (RD) vs. mild impairment = 8% (95% CI -5.1 to 20.1%); weight loss alone RD = 15% (3 to 27%); impaired, low anxiety/depression RD = 20% (9 to 31%); impaired with anxiety/depression RD = 36% (20 to 51%); global impairment RD= 36% (21 to 52%). Risk ratio estimates similarly showed that these classes had elevated risks relative to mild impairment (**Table 24**). In comparison, estimated 1-year mortality risk differences using frailty categories were as follows: pre-frail vs. robust RD = 11% (2 to 21%); frail vs. robust RD = 22% (12 to 32%).

In exploratory analyses assessing 1-year mortality for each impairment class stratified by high- and low-risk cancers, patients with high-risk cancers had greater mortality point estimates: high-risk cancer mortality estimate range = 29 to 75%; low-risk cancer estimate range = 3 to 32% (**Table 25**). The ordering of mortality estimates by latent class was similar to unstratified analyses for the low-risk subgroup. For the subgroup of patients with high-risk cancers, the mild impairment class and social support impairment class had similar rounded mortality estimates (29%), and the impaired with anxiety/depression class had the greatest estimated 1-year mortality (75%) followed by the global impairment class (62%); impaired, low anxiety/depression (41%); and weight loss alone (34%).

Exploratory analyses assessing 1-year mortality based on strata of cancer stage (IV vs. I-III) are provided in **Table 26.** The order of mortality estimates for patients with stage IV cancer were similar to the order for patients with high-risk cancer; the impaired with anxiety/depression

class had the greatest estimated mortality (62%) followed by the global impairment class (58%). The order of mortality estimates for patients with stage I-III cancer matched the order for unstratified analyses, but rounded estimates for the social support impairment class and weight loss alone class were the same (17%) and estimates for the impaired with anxiety/depression class and the global impairment class were similar (41 and 42%, respectively).

5.3.5. **Sensitivity Analyses**

For sensitivity analyses with single imputation of missing impairments, we were able to emulate the 6 latent impairment classes identified in primary analyses (**Table 27**); however, there were a few inherent differences with the resultant sensitivity analysis latent impairment classes. The new mild impairment class doubled in size (n=262, 44% of sample); became slightly more impaired with higher impairment probabilities for IADLs (37%, previously 19%) and weight loss impairment (41%, previously 25%); and was composed of a greater percentage of patients with frailty (32%, previously 20%, **Table 28**). The new social support impairment class (n=75, 13% of sample) had less weight loss impairment (35%, previously 45%) and again had no patients with frailty. The new weight loss alone class (n=89, 15% of sample) had slightly more impairment on IADLs (10%, previously 0%); reported no multimorbidity (previously 17%); and had similar frailty distributions as primary analyses.

The new impaired, low anxiety/depression impairment class (n=70, 12% of sample) had more impairment on IADLs (100%, previously 80%), ADLs (66%, previously 27%), ECOG-PS (41%, previously 17%), walking (67%, previously 38%), depression (4%, previously 0%), and cognition (11%, previously 4%). Patients assigned to this new impaired, low anxiety/depression class had a greater percentage of frailty compared to primary analyses (72%, previously 47%). The new impaired with anxiety/depression class (n=56, 9%) had worse impairment on ADLs (20%, previously 14%), ECOG-PS (36%, previously 28%), anxiety (100%, previously 88%), and polypharmacy (34%, previously 24%), but less weight loss impairment compared to primary

analyses (55%, previously 61%). Patients assigned to this new impaired class had similar distributions of frailty compared to primary analyses. The new global impairment class (n=48, 8%) had worse impairment on recent falls (83%, previously 60%, anxiety (54%, previously 42%), depression (46%, previously 40%), cognition (33%, previously 40%), and slightly less weight loss impairment (65%, previously 78%). Similar to primary analyses, the new global impairment class was composed entirely of patients with frailty.

Kaplan Meier survival curves were similar to primary analyses with 1-year mortality risks ranging from 21% to 50% for the new latent classes compared to 16-38% for frailty categories (**Figure 20, Table 28**). The order of mortality estimates differed from primary analyses: social support impairment class (21%, 95% CI 12 to 34%); mild impairment class (24%, 19 to 30%); weight loss alone class (28%, 19 to 40%); global impairment class (37%, 24 to 53%); impaired, low anxiety/depression (46%, 34 to 60%); impaired with anxiety/depression (50%, 36 to 65%). Stratified 1-year mortality estimates for the new impairment classes are provided in **Table 29** (high- vs. low-risk cancer) and **Table 30** (stage IV vs. stage I-III). Across strata, one-year mortality was generally greater for the two impaired classes and the global impairment class, compared to the mild impairment, social support impairment, and weight loss alone classes.

5.4. Discussion

In this registry sample of older adults with gastrointestinal cancers, we identified six latent impairment classes from patient responses on a geriatric assessment. Among patients with any geriatric assessment impairment, we specifically identified the following classes: mild impairment class; social support impairment class; weight loss alone class; impaired, low anxiety/depression class; impaired with anxiety/depression class; global impairment class. In primary and sensitivity analyses, mortality estimates for patients in the latter three impairment classes were greater than estimates for patients assigned to the mild impairment class. Estimates for the impaired classes and the global impairment class were also generally similar

or greater than mortality estimates when using the frailty categories. These classes could therefore be used to identify the most vulnerable patients.

The six geriatric assessment impairment classes also shed light on impairment patterns and can facilitate intervention planning to address impairment profiles. Individual impairments can be addressed directly with interventions. For example, cancer rehabilitation with occupational and physical therapy services for older adults with cancer could be used to address functional impairments and decrease disability caused by cancer and its treatments.[149] These therapy services are underutilized[150] which may be problematic considering that unaddressed cancer- and treatment-related conditions like fatigue, lymphedema, and chemotherapy-induced peripheral neuropathy could precipitate life-long disability.[151,152] Additionally, weight loss and social support impairment in older adults with cancer could be addressed with dietitian and social worker services, respectively.[153,154] Depression can be also be addressed through pharmacotherapy or psychotherapy, and referrals to psychiatry may now involve structured psychosocial interventions to support older adults with cancer.[155-157]

Our research highlights the importance of packaged interventions to support older adult patients with multiple impaired health domains. Planning multiple support services for co-occurring impairments requires awareness of patterns, and coordination and continuity between providers and services to ensure that impairments are addressed together and not in isolation. For older adults with gastrointestinal cancer, nutrition or dental intervention may need to be coupled with occupational or physical therapy services to address weight loss, malnutrition, and functional deficits. Other impairment profiles may need to be addressed with added social support intervention or therapy to support patients with anxiety or depression.

These results and approach build off of the work from the ELCAPA study. We focused on patients with gastrointestinal cancers and restricted our sample to older patients who reported at least one impairment in order to focus on identifying latent impairment classes. Patients with zero impairments represent a clear healthy class on their own, and thus we did not

include them in an approach designed to identify latent patterns. Additionally, we incorporated all available geriatric assessment impairments which included impairments that were excluded in the ELCAPA study, such as IADL, walking, falls, and anxiety.

In terms of the resultant classes, the ELCAPA study identified a malnourished class with 66% probability of reporting nutrition impairment, whereas our study identified a weight-loss-alone class in which 100% of assigned patients had weight loss impairment. The 1-year mortality estimate for our weight loss alone class was lower than estimated mortality for the ELCAPA malnourished class (24% vs. 40%) which may be a result of differences in study inclusion criteria, impairment measurement, and composition of the resultant classes. For patients with gastrointestinal cancers, a population in which disease course may directly impact malnutrition and weight loss, our results are more informative to understanding vulnerability associated with weight loss alone or weight loss combined with other impairments. Our study was also able to identify a class characterized by social support impairment which had relatively low mortality among the impairment classes.

Other noteworthy health profiles have been previously identified by Balducci and Extermann[56] and a working group of the International Society of Geriatric Oncology (SIOG).[57] These categories were derived based on conceptual understandings of aging and frailty and clinical expertise. Balducci and Extermann proposed that following three groups could be recognized from comprehensive geriatric assessment: (1) functionally independent and without serious comorbidity, (2) dependence on at least one IADL and/or presence of one or two comorbid conditions, (3) frail patients.[56] The SIOG working group focused on older men with prostate cancer and recommended evaluation of comorbidities using the Cumulative Illness Score Rating-Geriatrics (CISR-G) scale, dependence status using IADL and ADL, and nutritional status based on 3-month weight loss.[57] The SIOG group identified the following four health status categories: (1) healthy or fit patients with no serious comorbidity, no functional dependence, and no malnutrition; (2) vulnerable patients with dependence in IADL but no

dependence in ADL, or presence of one comorbid uncontrolled condition, or risk of malnutrition; (3) frail patients with ADL impairment, or two or more uncontrolled comorbid conditions, or severe malnutrition; (4) 'too sick' patients with poor health status from a combination of different impairments. In these categorizations, both IADL and ADL assessment were included to capture moderately impaired and strongly impaired patients.

Our latent classes also highlighted the importance of including both IADL and ADL assessments. The prevalence of IADL impairment was greater than ADL impairment, and three classes (impaired, low anxiety/depression; impaired with anxiety/depression; global impairment) had IADL impairment probabilities greater than 50%. Only the global impairment class had high ADL impairment probability. Thus, while ADL impairment may identify the most vulnerable patients, the inclusion of other functional domains such as IADLs allowed us to identify and differentiate patients with moderate impairment. Our study also builds upon these groupings by incorporating other domains that are recommended for evaluation in a comprehensive assessment including anxiety, depression, cognition, social support, and social interference.

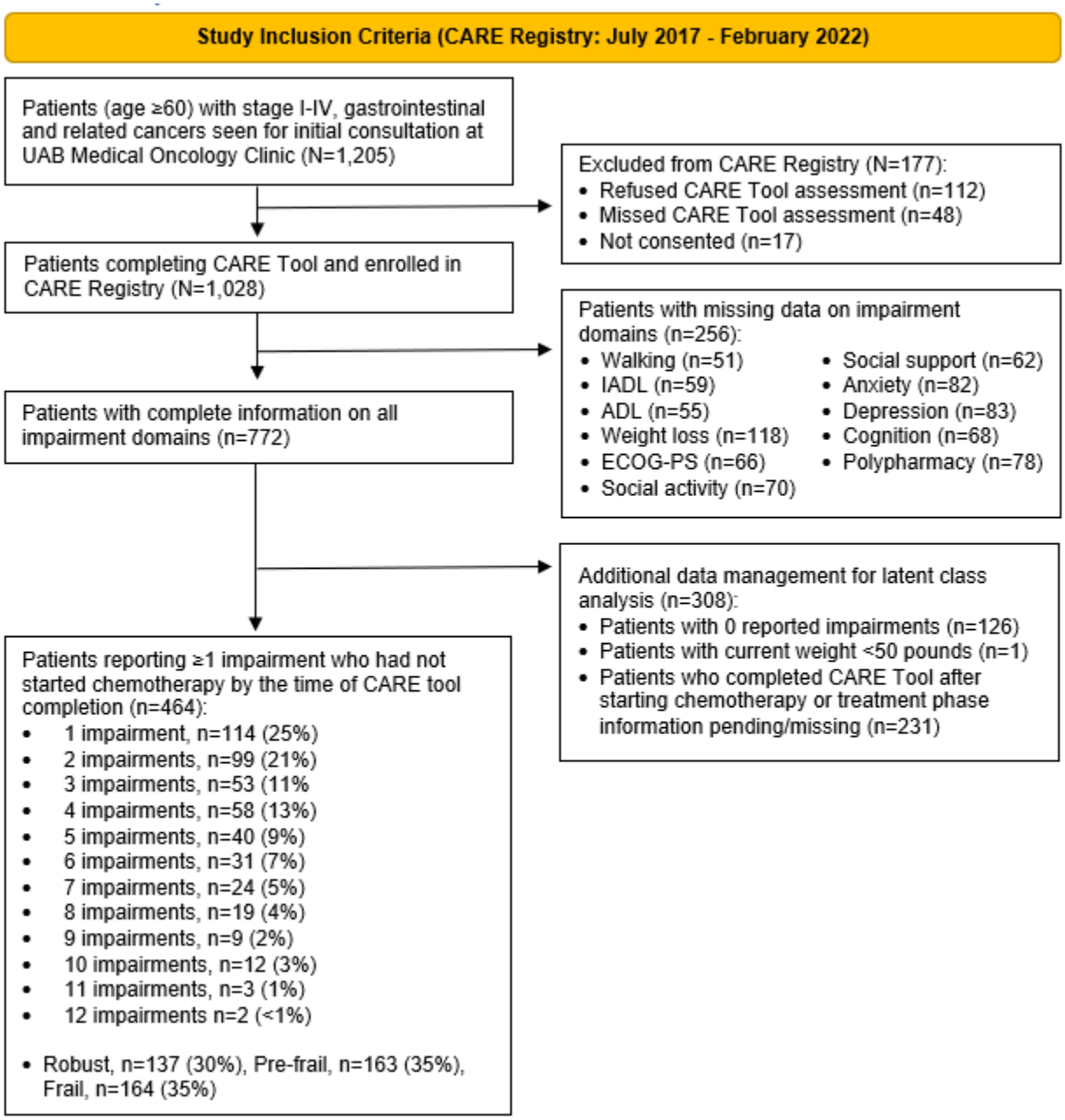
Results from this analysis are limited in their generalizability to other patient populations with gastrointestinal cancers due to the CARE Registry setting at an academic healthcare site located in southeastern US. There were also limitations to internal validity. For primary analyses, we restricted analyses to patients who had information on all 13 impairment domains, because we could not take the absence of data to reasonably mean the absence of an impairment. This limited our sample size for LCA and may exclude relatively healthy patients who skipped questions or patients with poor health who failed to report impairment. In our sensitivity analyses, results still demonstrated high vulnerability for patients assigned to the impaired, low anxiety/depression class; impaired with anxiety/depression class; and the global impairment class. Additionally, impairment domains were assessed through a self-reported geriatric assessment that was completed by the patient alone which is more subject to

information bias than if the domains were assessed by clinical staff using a comprehensive geriatric assessment.

Despite these limitations, there were a number of study strengths including the use of the fully patient-reported CARE tool which made it feasible to assess a large patient population as opposed to more comprehensive but more resource-dependent clinical assessments. Additionally, we included all available geriatric assessment impairments which may better leverage LCA's clustering capabilities for identifying unique classes from geriatric assessment domains. We included anxiety and multiple functional domains (i.e., IADLs, ADLs, walking, falls, activity level) which were not all considered in previous health profiles.

In summary, we identified 6 unique impairment profiles using geriatric assessment and LCA that go beyond frailty classification in describing impairment patterns for patients with gastrointestinal cancer. Knowledge on the co-occurrence of geriatric assessment impairments in this population can facilitate intervention selection and intervention packaging to support older adults as they undergo cancer treatment. Furthermore, these impairment classes may help clinicians identify key components of geriatric assessments that could be used in shortened assessments.

Figure 18. Study Inclusion Criteria for Aim 2



ADLs = Activities of daily living, CARE = Cancer and Aging Resilience Evaluation, ECOG-PS = Eastern Cooperative Oncology Group Performance Status, IADL = Instrumental activities of daily living, UAB = University of Alabama at Birmingham.

Table 21. Characteristics of the CARE Registry Study Sample and Latent Impairment Classes at Enrollment (2017-2021, N=464)

Characteristics, n (%)	Overall Sample (n=464)	Class 1 Mild impairment (n=130)	Class 2 Social support impairment (n=56)	Class 3 Weight loss alone (n=72)	Class 4 Impaired, low anxiety/depression (n=105)	Class 5 Impaired with anxiety/depression (n=51)	Class 6 Global Impairment (n=50)
Age (median, IQR)	69 (64-75)	70 (65-76)	68 (62-75)	67 (63-73)	70 (64-75)	68 (64-74)	71 (65-76)
Gender (% female)	42.7%	44.6%	37.5%	44.4%	43.8%	45.1%	36.0%
Race							
White / Caucasian	359 (77.4)	107 (82.3)	49 (87.5)	57 (79.2)	72 (68.6)	36 (70.6)	38 (76.0)
Black / African American	93 (20.0)	21 (16.2)	6 (10.7)	12 (16.7)	28 (26.7)	15 (29.4)	11 (22.0)
Asian	6 (1.3)	0 (0.0)	1 (1.8)	2 (2.8)	2 (1.9)	0 (0.0)	1 (2.0)
American Indian / Alaska Native	2 (0.4)	(0.0)	0 (0.0)	0 (0.0)	2 (1.9)	0 (0.0)	0 (0.0)
Other / unknown	4 (0.9)	2 (1.5)	0 (0.0)	1 (1.4)	1 (1.0)	0 (0.0)	0 (0.0)
Education level							
Less than high school	69 (14.9)	23 (17.7)	3 (5.4)	5 (6.9)	20 (19.1)	10 (19.6)	8 (16.0)
High school graduate	218 (47.0)	60 (46.2)	26 (46.4)	34 (47.2)	47 (44.8)	23 (45.1)	28 (56.0)
Associate / bachelors	119 (25.7)	31 (23.9)	17 (30.4)	26 (36.1)	26 (24.8)	10 (19.6)	9 (18.0)
Advanced degree	51 (11.0)	16 (12.3)	9 (16.1)	7 (9.7)	10 (9.5)	5 (9.8)	4 (8.0)
Unknown	7 (1.5)	0 (0.0)	1 (1.8)		2 (1.9)	3 (5.9)	1 (2.0)
Marital status							
Single, never married	29 (6.3)	7 (5.4)	3 (5.4)	2 (2.8)	13 (12.4)	2 (3.9)	2 (4.0)
Widowed / divorced / separated	155 (33.4)	43 (33.1)	31 (55.4)	13 (18.1)	22 (21.0)	28 (54.9)	18 (36.0)
Married	272 (58.6)	78 (60.0)	21 (37.5)	57 (79.2)	67 (63.8)	19 (37.3)	30 (60.0)
Unknown	8 (1.7)	2 (1.5)	1 (1.8)	0 (0.0)	3 (2.9)	2 (3.9)	0 (0.0)
Cancer Type							
Low risk	233 (50.2)	76 (58.5)	36 (64.3)	30 (41.7)	42 (40.0)	27 (52.9)	22 (44.0)
High risk	231 (49.8)	54 (41.5)	20 (35.7)	42 (58.3)	63 (60.0)	24 (47.1)	28 (56.0)
Cancer Stage							
I-III	268 (57.8)	88 (67.7)	41 (73.2)	37 (51.4)	49 (46.7)	30 (58.8)	23 (46.0)
IV	196 (42.2)	42 (32.3)	15 (26.8)	35 (48.6)	56 (53.3)	21 (41.2)	27 (54.0)
Chemotherapy treatment (current)							
1	343 (73.9)	102 (78.5)	43 (76.8)	54 (75.0)	81 (77.1)	31 (60.8)	32 (64.0)
2-4	10 (2.2)	4 (3.1)	2 (3.6)	1 (1.4)	2 (1.9)	1 (2.0)	0 (0.0)
≥5	62 (13.4)	13 (10.0)	5 (8.9)	9 (12.5)	10 (9.5)	11 (21.6)	14 (28.0)
Unknown	49 (10.6)	11 (8.5)	6 (10.7)	8 (11.1)	12 (11.4)	8 (15.7)	4 (8.0)
BMI Category							
Underweight	21 (4.5)	2 (1.5)	2 (3.6)	3 (4.2)	5 (4.8)	3 (5.9)	6 (12.0)
Normal weight	169 (36.4)	34 (26.2)	24 (42.9)	30 (41.7)	37 (35.2)	29 (56.9)	15 (30.0)
Overweight	142 (30.6)	47 (36.2)	15 (26.8)	25 (34.7)	28 (26.7)	11 (21.6)	16 (32.0)
Obese	124 (26.7)	45 (34.6)	14 (25.0)	13 (18.1)	31 (29.5)	8 (15.7)	13 (26.0)

Unknown	8 (1.7)	2 (1.5)	1 (1.8)	1 (1.4)	4 (3.8)	0 (0.0)	0 (0.0)
Frailty							
Robust	137 (29.5)	36 (27.7)	47 (83.9)	42 (58.3)	10 (9.5)	2 (3.9)	0 (0.0)
Pre-frail	163 (35.1)	68 (52.3)	9 (16.1)	29 (40.3)	45 (42.9)	12 (23.5)	0 (0.0)
Frail	164 (35.3)	26 (20.0)	0 (0.0)	1 (1.4)	50 (47.6)	37 (72.6)	50 (100.0)
Co-morbidities							
Other cancers or leukemia	102 (22.0)	33 (25.4)	9 (16.1)	16 (22.2)	21 (20.0)	12 (23.5)	11 (22.0)
Arthritis or rheumatism	178 (38.4)	71 (54.6)	13 (23.2)	17 (23.6)	37 (35.2)	20 (39.2)	20 (40.0)
Glaucoma	33 (7.1)	9 (6.9)	1 (1.8)	4 (5.6)	10 (9.5)	4 (7.8)	5 (10.0)
Emphysema or chronic bronchitis	45 (9.7)	15 (11.5)	2 (3.6)	3 (4.2)	11 (10.5)	5 (9.8)	9 (18.0)
High blood pressure	294 (63.4)	101 (77.7)	28 (50.0)	42 (58.3)	65 (61.9)	25 (49.0)	33 (66.0)
Heart disease	99 (21.3)	43 (33.1)	3 (5.4)	7 (9.7)	22 (21.0)	7 (13.7)	17 (34.0)
Circulation trouble in arms/legs	99 (21.3)	34 (26.2)	3 (5.4)	6 (8.3)	22 (21.0)	11 (21.6)	23 (46.0)
Diabetes	158 (34.1)	61 (46.9)	12 (21.4)	17 (23.6)	41 (39.1)	8 (15.7)	19 (38.0)
Stomach or intestinal disorders	178 (38.4)	58 (44.6)	12 (21.4)	20 (27.8)	39 (37.1)	23 (45.1)	26 (52.0)
Osteoporosis	51 (11.0)	16 (12.3)	5 (8.9)	3 (4.2)	15 (14.3)	7 (13.7)	5 (10.0)
Chronic liver or kidney disease	87 (18.8)	27 (20.8)	7 (12.5)	10 (13.9)	22 (21.0)	9 (17.7)	12 (24.0)
Stroke	36 (7.8)	10 (7.7)	1 (1.8)	5 (6.9)	7 (6.7)	4 (7.8)	9 (18.0)
Depression	91 (19.6)	22 (16.9)	2 (3.6)	6 (8.3)	12 (11.4)	29 (56.9)	20 (40.0)

BMI = body mass index, CARE = Cancer and Aging Resilience Evaluation, IQR = interquartile range.

Table 22. Accuracy and Fit of Latent Class Models with One to Eight Class (N=464)

No. of Classes	LL	AIC	BIC	ABIC	p-value BLRT	Entropy
1	-3300	2066	2120	2078	<0.001	1.00
2	-2991	1477	1588	1503	<0.001	0.83
3	-2945	1411	1581	1451	<0.001	0.78
4	-2898	1347	1574	1400	0.002	0.77
5	-2873	1323	1609	1390	0.005	0.79
6	-2850	1306	1650	1387	0.066	0.79
7	-2832	1298	1700	1392	0.052	0.81
8	-2814	1290	1750	1398	0.025	0.80

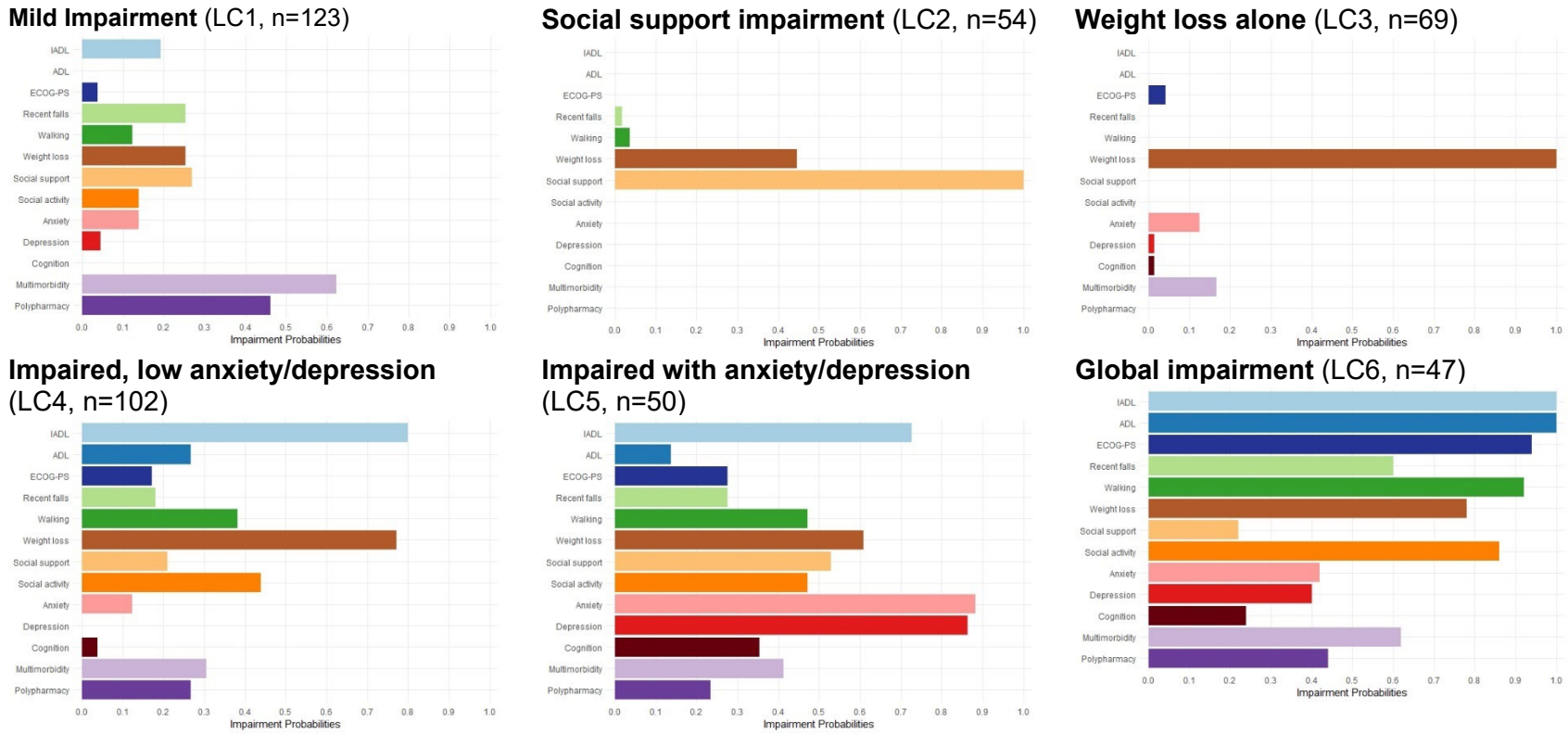
AIC = Akaike information criterion, ABIC = adjusted Bayesian information criterion, BIC = Bayesian information criterion, BLRT = bootstrap likelihood ratio test, LL = log likelihood.

Table 23. Item Impairment Probabilities for Each Latent Class and the Overall CARE Registry Sample (N=464)

Geriatric Assessment Impairments	Impairment Prevalence n (%)	Class 1 Mild impairment (n=130)	Class 2 Social support impairment (n=56)	Class 3 Weight loss alone (n=72)	Class 4 Impaired, low anxiety/depression (n=105)	Class 5 Impaired with anxiety/depression (n=51)	Class 6 Global Impairment (n=50)
IADL	196 (42.2)	0.192	0.000	0.000	0.800	0.726	1.000
ADL	85 (18.3)	0.000	0.000	0.000	0.267	0.137	1.000
ECOG-PS	87 (18.8)	0.039	0.000	0.042	0.171	0.275	0.940
Recent falls	97 (20.9)	0.254	0.018	0.000	0.181	0.275	0.600
Walking	128 (27.6)	0.123	0.036	0.000	0.381	0.471	0.920
Weight loss	281 (60.6)	0.254	0.446	1.000	0.771	0.608	0.780
Social support	151 (32.5)	0.269	1.000	0.000	0.210	0.529	0.220
Social activity	131 (28.2)	0.139	0.000	0.000	0.438	0.471	0.860
Anxiety	106 (22.8)	0.139	0.000	0.125	0.124	0.882	0.420
Depression	71 (15.3)	0.046	0.000	0.014	0.000	0.863	0.400
Cognition	35 (7.5)	0.000	0.000	0.014	0.038	0.353	0.240
Multimorbidity	177 (38.2)	0.623	0.000	0.167	0.305	0.412	0.620
Polypharmacy	122 (26.3)	0.462	0.000	0.000	0.267	0.235	0.440
Posterior Probability of Class Membership	-----	0.815	0.904	0.832	0.800	0.916	0.913

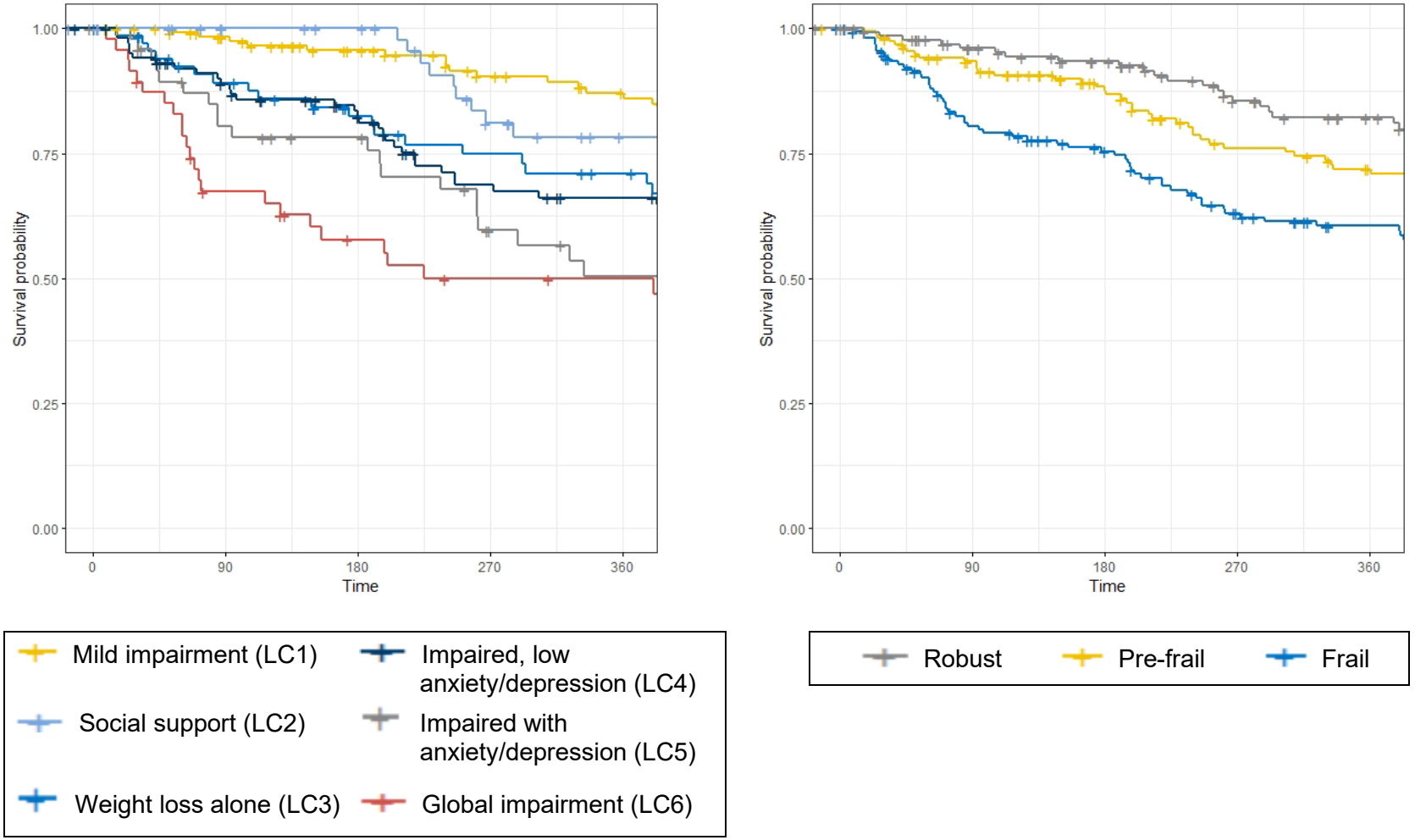
ADL = Activities of daily living, CARE = Cancer and Aging Resilience Evaluation, ECOG-PS = Eastern Cooperative Oncology Group Performance Status, IADL = Instrumental activities of daily living.

Figure 19. Item Impairment Probabilities for Each Latent Class (N=464)



ADL = activities of daily living, ECOG-PS = Eastern Cooperative Oncology Group Performance Status, IADL = instrumental activities of daily living, LC = latent class.

Figure 20. Kaplan-Meier Curves for 1-Year Mortality by Latent Impairment Class and by Frailty Status (CARE Registry Sample, 2017-2021, N=445)



CARE = Cancer and Aging Resilience Evaluation, LC = latent class.

Table 24. One-Year Mortality Results by Latent Impairment Class Membership and by Frailty Status (CARE Registry Sample, 2017-2021, N=445)

Latent Class	N	Frailty Prevalence (%)			1-Year Mortality	Risk Difference	Risk Ratio
		Robust	Pre-frail	Frail	% (95% CI)	% (95% CI)	(95% CI)
LC1: Mild impairment	123	28.5	52.0	19.5	14.1 (8.6, 22.7)	Reference	Reference
LC2: Social support impairment	54	83.3	16.7	0.0	21.6 (11.8, 37.4)	7.5 (-5.1, 20.1)	1.53 (0.90, 2.60)
LC3: Weight loss alone	69	59.4	39.1	1.5	28.9 (19.0, 42.5)	14.9 (2.5, 27.2)	2.06 (1.37, 3.09)
LC4: Impaired, low anxiety/depression	102	9.8	43.1	47.1	34.0 (25.1, 45.1)	19.9 (8.9, 31.0)	2.42 (1.64, 3.56)
LC5: Impaired with anxiety/depression	50	4.0	24.0	72.0	49.6 (35.1, 66.3)	35.5 (20.4, 50.7)	3.53 (2.27, 5.48)
LC6: Global impairment	47	0.0	0.0	100.0	50.4 (36.5, 66.1)	36.3 (20.8, 51.9)	3.58 (2.37, 5.40)

Frailty Status	N	Latent Class Prevalence (%)						1-Year Mortality	Risk Difference	Risk Ratio
		LC1	LC2	LC3	LC4	LC5	LC6	% (95% CI)	% (95% CI)	(95% CI)
Robust	133	26.3	33.8	30.8	7.5	1.5	0.0	17.8 (11.7, 26.7)	Reference	Reference
Pre-frail	156	41.0	5.8	17.3	28.2	7.7	0.0	29.1 (22.0, 37.9)	11.3 (1.6, 20.9)	1.63 (1.17, 2.27)
Frail	156	15.4	0.0	0.6	30.8	23.1	30.1	39.6 (31.9, 48.4)	21.8 (11.7, 31.8)	2.22 (1.62, 3.04)

CARE = Cancer and Aging Resilience Evaluation, CI = confidence interval, LC = latent class.

Table 25. Assessment of 1-Year Mortality for Latent Impairment Classes Identified in the CARE Registry Sample, Stratified by Cancer Type (2017-2021, N=445)*

			1-Year Mortality by Cancer Type (%)		
Latent Class	**N**	**Overall 1-year Mortality (%)**	**High-risk (95% CI)**	**Low-risk (95% CI)**	**Difference (High vs. Low, 95% CI)**
LC1: Mild impairment	123	14.1	28.5 (17.3, 44.9)	3.3 (0.8, 12.4)	25.3 (12.1, 38.5)
LC2: Social support impairment	54	21.6	29.4 (13.4, 56.9)	15.8 (6.2, 37.0)	13.6 (-9.9, 37.0)
LC3: Weight loss alone	69	28.9	34.0 (20.8, 52.3)	21.0 (9.2, 43.5)	13.0 (-7.8, 33.9)
LC4: Impaired, low anxiety/ depression	102	34.0	40.6 (28.8, 55.0)	23.3 (12.3, 41.8)	17.3 (-0.5, 35.1)
LC5: Impaired with anxiety/depression	50	49.6	74.7 (52.9, 91.8)	29.8 (14.5, 55.1)	44.8 (20.1, 69.6)
LC6: Global impairment	47	50.4	61.5 (43.3, 79.9)	32.4 (16.1, 58.4)	29.1 (1.4, 56.8)

CARE = Cancer and Aging Resilience Evaluation, CI = confidence interval.

*High-risk cancers = pancreatic, hepatobiliary, esophageal cancers low-risk cancers = colorectal, gastrointestinal stromal tumors (GIST), neuroendocrine tumors, and other gastrointestinal cancers.

Table 26. Assessment of 1-Year Mortality for Latent Impairment Classes Identified in the CARE Registry Sample, Stratified by Cancer Stage (2017-2021, N=445)

			1-Year Mortality by Cancer Stage (%)		
Latent Class	**N**	**Overall 1-year Mortality (%)**	**Stage IV (95% CI)**	**Stage I-III (95% CI)**	**Difference (Stage IV vs. I-III, 95% CI)**
LC1: Mild impairment	123	14.1	12.9 (5.0, 31.0)	14.6 (8.1, 25.5)	-1.7 (-14.6, 11.2)
LC2: Social support impairment	54	21.6	31.9 (13.2, 64.5)	17.2 (7.6, 36.6)	14.6 (-12.5, 41.7)
LC3: Weight loss alone	69	28.9	42.1 (26.4, 62.2)	17.0 (7.4, 36.3)	25.1 (4.1, 46.0)
LC4: Impaired, low anxiety/ depression	102	34.0	44.9 (32.1, 60.0)	20.7 (10.9, 37.3)	24.2 (6.7, 41.7)
LC5: Impaired with anxiety/depression	50	49.6	61.8 (39.7, 83.9)	40.5 (23.3, 63.7)	21.3 (-6.1, 48.7)
LC6: Global impairment	47	50.4	58.1 (39.6, 77.7)	41.9 (23.4, 66.9)	16.2 (-12.1, 44.5)

CARE = Cancer and Aging Resilience Evaluation, CI = confidence interval, LC = latent class.

Table 27. Sensitivity Analyses—Item Impairment Probabilities for Each Latent Class and the Overall CARE Registry Sample (N=600)*

Geriatric Assessment Impairments	Impairment Prevalence n (%)	Sensitivity Analysis Prevalence n (%)	Class 1 "Mild impairment" (n=262)	Class 2 "Social support impairment" (n=75)	Class 3 "Weight loss alone" (n=89)	Class 4 "Impaired, low anxiety/depression" (n=70)	Class 5 "Impaired with anxiety/depression" (n=56)	Class 6 "Global Impairment" (n=48)
IADL	196 (42.2)	267 (44.5)	0.370	0.000	0.101	1.000	0.768	1.000
ADL	85 (18.3)	128 (21.3)	0.080	0.027	0.000	0.657	0.196	1.000
ECOG-PS	87 (18.8)	112 (18.7)	0.057	0.000	0.056	0.414	0.357	0.896
Recent falls	97 (20.9)	138 (23.0)	0.279	0.027	0.000	0.100	0.286	0.833
Walking	128 (27.6)	170 (28.3)	0.199	0.000	0.000	0.671	0.500	0.896
Weight loss	281 (60.6)	330 (55.0)	0.405	0.347	1.000	0.671	0.554	0.646
Social support	151 (32.5)	197 (32.8)	0.279	1.000	0.000	0.186	0.446	0.229
Social activity	131 (28.2)	164 (27.3)	0.191	0.000	0.056	0.600	0.500	0.813
Anxiety	106 (22.8)	132 (22.0)	0.149	0.000	0.124	0.000	1.000	0.542
Depression	71 (15.3)	89 (14.8)	0.053	0.000	0.023	0.043	0.857	0.458
Cognition	35 (7.5)	50 (8.3)	0.019	0.000	0.023	0.114	0.339	0.333
Multimorbidity	177 (38.2)	225 (37.5)	0.588	0.000	0.000	0.329	0.375	0.563
Polypharmacy	122 (26.3)	153 (25.5)	0.328	0.067	0.078	0.143	0.339	0.542
Posterior Probability of Class Membership	-----	-----	0.881	0.881	0.799	0.796	0.890	0.901

ADL = activities of daily living, CARE = Cancer and Aging Resilience Evaluation, ECOG-PS = Eastern Cooperative Oncology Group Performance Status, IADL = instrumental activities of daily living, LC = latent class.

*Class names are listed in quotations because they emulate latent classes from primary analyses but may be composed of different patients.

Figure 21. Sensitivity Analyses—Kaplan-Meier Curves for 1-Year Mortality by Latent Impairment Class and by Frailty Status (CARE Registry Sample, 2017-2021, N=579)

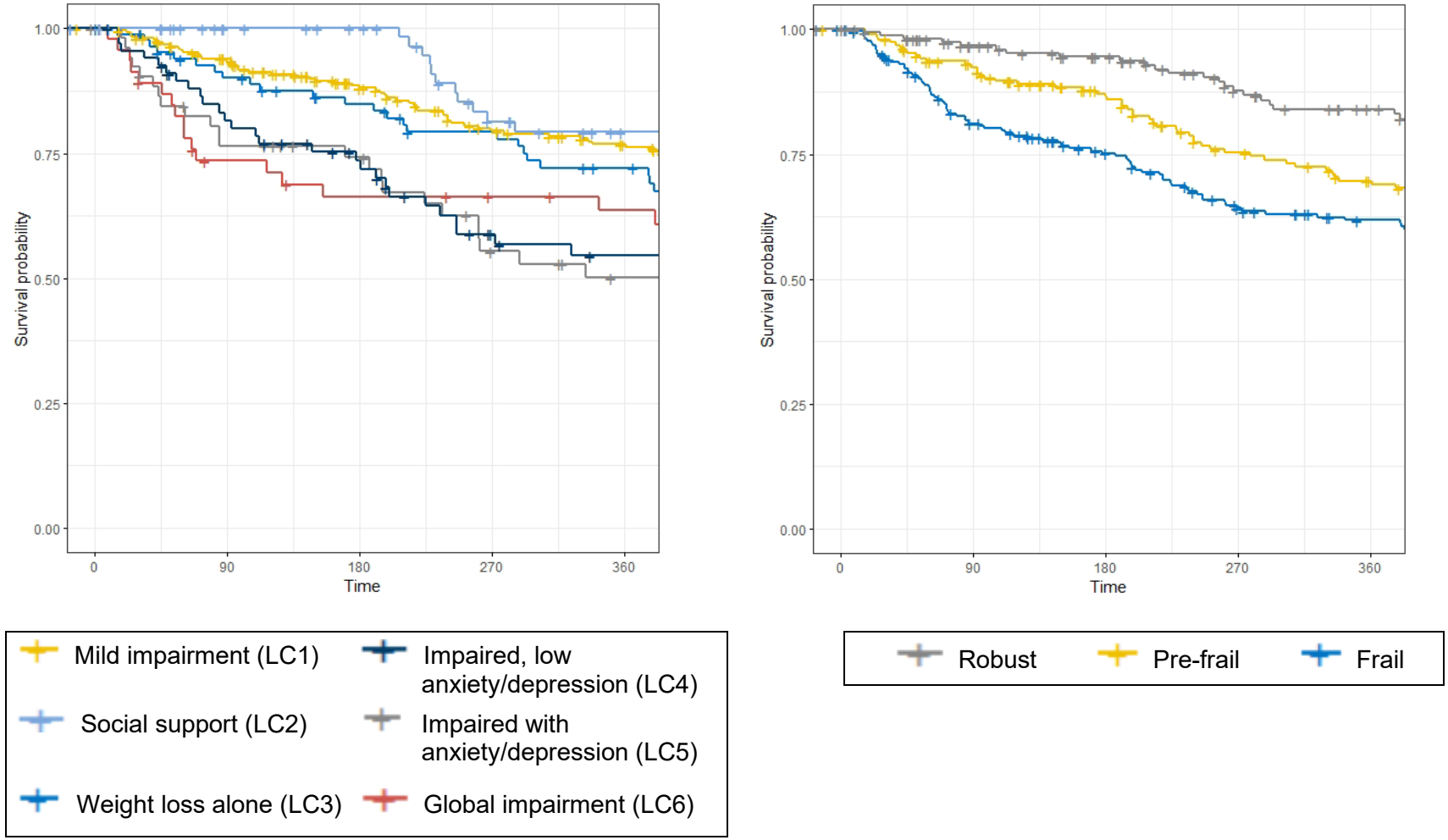


Table 28. Sensitivity Analyses—One-Year Mortality Results by Latent Impairment Class Membership and by Frailty Status (CARE Registry Sample, 2017-2021, N=579)

		Frailty Prevalence (%)				1-Year	Risk	Risk
Latent Class	**N**	**Robust**	**Pre-frail**	**Frail**	**Unknown***	**Mortality (%)**	**Difference (%)**	**Ratio**
LC1: Mild impairment	253	19.8	47.0	32.4	0.8	23.8	Reference	Reference
LC2: Social support impairment	73	78.1	17.8	0.0	4.1	20.7	-3.1	0.87
LC3: Weight loss alone	85	56.5	37.7	3.5	2.4	28.1	4.3	1.18
LC4: Impaired, low anxiety/depression	68	2.9	23.5	72.1	1.5	46.1	22.3	1.94
LC5: Impaired with anxiety/depression	54	1.9	20.4	75.9	1.9	49.9	26.1	2.10
LC6: Global impairment	46	0.0	0.0	100.0	0.0	36.5	12.8	1.54

		Latent Class Prevalence (%)						1-Year	Risk	Risk
Frailty Status	**N**	**LC1**	**LC2**	**LC3**	**LC4**	**LC5**	**LC6**	**Mortality (%)**	**Difference (%)**	**Ratio**
Robust	158	30.4	36.1	1.3	31.7	0.6	0.0	16.0	Reference	Reference
Pre-frail	191	16.8	6.8	8.4	62.3	5.8	0.0	31.2	15.2	1.95
Frail	221	1.4	0.0	22.2	37.1	18.6	20.8	38.3	22.3	2.40

CARE = Cancer and Aging Resilience Evaluation, CI = confidence interval, LC = latent class.

*Patients with unknown frailty status (n=9) responded to fewer than 24 items on the CARE tool.

Table 29. Sensitivity Analyses— Assessment of 1-Year Mortality for Latent Impairment Classes Identified in the CARE Registry Sample, Stratified by Cancer Type (2017-2021, N=579)*

Latent Class	N	Primary Analyses: Overall 1-year Mortality (%)	Sensitivity Analyses: Overall 1-year Mortality (%)	Sensitivity Analyses: 1-Year Mortality by Cancer Type (%)		
				High-risk Cancer	Low-risk Cancer	Difference (High vs. Low)
LC1: Mild impairment	253	14.1	23.8	38.6	9.6	29.0
LC2: Social support impairment	73	21.6	20.7	27.3	15.8	11.5
LC3: Weight loss alone	85	28.9	28.1	28.0	28.0	0.0
LC4: Impaired, low anxiety/ depression	68	34.0	46.1	47.1	44.0	3.1
LC5: Impaired with anxiety/depression	54	49.6	49.9	65.1	31.1	34.0
LC6: Global impairment	46	50.4	36.5	47.9	23.7	24.2

CARE = Cancer and Aging Resilience Evaluation, CI = confidence interval, LC = latent class.

*High-risk cancers = pancreatic, hepatobiliary, esophageal cancers; low-risk cancers = colorectal, gastrointestinal stromal tumors (GIST), neuroendocrine tumors, and other gastrointestinal cancers.

Table 30. Sensitivity Analyses—Assessment of 1-Year Mortality for Latent Impairment Classes Identified in the CARE Registry Sample, Stratified by Cancer Stage (2017-2021, N=579)

Latent Class	N	Primary Analyses: Overall 1-year Mortality (%)	Sensitivity Analyses: Overall 1-year Mortality (%)	Sensitivity Analyses: 1-Year Mortality by Cancer Type (%)		
				Stage IV	Stage I-III	Difference (Stage IV vs. I-III)
LC1: Mild impairment	253	14.1	23.8	31.5	18.7	12.9
LC2: Social support impairment	73	21.6	20.7	39.2	13.3	25.8
LC3: Weight loss alone	85	28.9	28.1	37.6	17.5	20.0
LC4: Impaired, low anxiety/ depression	68	34.0	46.1	51.2	42.3	9.0
LC5: Impaired with anxiety/depression	54	49.6	49.9	63.5	36.5	27.0
LC6: Global impairment	46	50.4	36.5	52.5	15.7	36.8

CARE = Cancer and Aging Resilience Evaluation, CI = confidence interval, LC = latent class.

CHAPTER 6: CONCLUSIONS

6.1. Main Findings

The main objectives of this study were:

(1) To assess the performance of SMD as a screening tool for frailty in older adults with cancer and to compare performance between men and women with and without comorbid diabetes.

(2) To identify impairment pattern profiles in patients with gastrointestinal malignancies using LCA, and to describe profiles.

For the first objective, we report that SMD performed poorly when used alone to classify frailty. Performance was similarly weak for each gender-diabetes subset, although classification may be better when SMD is used to screen men with diabetes. In order to identify most patients with frailty using SMD, a high cut-off point would need to be selected. However, even high cut-off points (e.g., gender-specific third quartile cut-offs) would miss 11-24% of patients with frailty, and it would not effectively narrow the patient population who should undergo further geriatric assessment due to the inclusion of many false-positives results.

For the second objective, we identified 6 geriatric assessment impairment classes using LCA, and these classes were distinctly associated with mortality. We labeled the resultant classes as follows: mild impairment class; social support impairment class; weight loss alone class; (moderately) impaired, low anxiety/depression; (moderately) impaired with anxiety/depression; global impairment. Relative to the mild impairment class, we report that estimated 1-year mortality was elevated for the other impairment classes. Additionally, mortality

estimates using the latent impairment classes had a wider range compared to estimates using frailty classifications, suggesting their high utility for risk stratification. For a gastrointestinal cancer population, malnutrition and weight loss may be expected, but we identified relevant impairment patterns that go beyond weight loss.

These findings provide clinically meaningful evidence for the evaluation of frailty and impairments in older adults with cancer. The screening performance results shed light on the performance of SMD alone to classify frailty and suggest that more work is needed to improve performance before clinical implementation. Additionally, these results highlight one of many possible subgroups for which screening performance may be particularly adept at classifying frailty—older adult men with diabetes. From LCA, we identified impairment profiles that are distinct in their association with adverse outcomes which helps to synthesize the numerous health domains that are recommended for evaluation in geriatric assessments and to plan multi-component interventions to support older adults with cancer.

6.2. Study Strengths

This dissertation work has a number of study strengths. We used the CARE registry which is a rich data source that leverages a self-reported geriatric assessment to identify impairments and frailty. This assessment can feasibly evaluate a large population of patients with cancer and does not rely on extensive clinical measurement. Additionally, patients completed the CARE tool before being approached to enroll in the registry; therefore, reporting biases may have been minimized. For LCA, we leveraged the multiple health domains assessed in the CARE tool and did not pre-screen impairments used as latent class indicators. The registry also included CT scans analyzed using an auto-segmentation approach which reduces labor and dependence on manual segmentation.

6.3. Study Limitations

Despite the numerous study strengths, there are limitations to consider. The generalizability of the CARE registry sample should be noted as UAB is an academic healthcare site located in southeastern US. Patients were predominately White/Caucasian followed by Black/African American, and there were few enrollees who were Asian, indigenous, or who belonged to other race and ethnic groups. Our analyses were also limited to patients who had CT scans (Aim 1) and complete information on impairments (Aim 2) which limited the size of the analytic cohort. The CARE tool was also a self-reported geriatric assessment which be subject to information bias. Additionally, the registry does not capture undiagnosed diabetes, diabetes duration, treatments, or physical activity; therefore, these factors which may impact diabetes severity and frailty remain unexplored.

6.4. Future Directions

In our first aim, we evaluated the impact of diabetes on SMD screening performance for classifying frailty and reported poor performance overall. Future work should evaluate patient and physician preferences for geriatric assessment to better understand the clinical and resource impacts of different cut-off criteria. Additionally, future studies should focus on whether additional clinical criteria could be incorporated with SMD to improve frailty classification. This could be specific impairment items on the geriatric assessment (e.g., IADL scores) or laboratory results (e.g., renal function or serum albumin), and machine learning methodologies could be leveraged to identify combinations of clinical data that could improve screening performance. Also, like with our evaluation of patients with diabetes, other patient subgroups should be evaluated to see if SMD performs better. This includes extending this research to larger, more diverse racial and ethnic patient samples where diabetes and obesity may be more prevalent and linked with frailty. Further, while we assessed the performance of SMD in classifying baseline frailty, future research should explore how SMD performs in identifying patients who

experience chemotoxicities. This may be a promising avenue for SMD research as body and muscle composition have been shown to be associated with chemotherapy clearance and peak concentrations[99] and thus should be explored for possible incorporation into dosing algorithms. Finally, while our frailty index scoring was based on the principles of deficit accumulation, further work should explore how SMD performs in classifying strictly physical and functional frailty phenotypes.

To build from our Aim 2 work, future research should explore the association of identified impairment classes with intermediate outcomes such as chemotherapy dose reductions, alterations, and discontinuations. These treatment adherence and persistence outcomes impact the delivery of chemotherapy and impact treatment success and survival. Further, like with Aim 1, it is important to evaluate the validity of these classes in forecasting outcomes in larger and more diverse patient samples.

6.5. Public Health Impact

Older adults are greatly underrepresented in clinical trials[158] which impacts treatment guidelines for these populations, and frailty is one medical conceptualization that can help to inform treatment decision making. This research contributes to the evidence base for assessing and understanding frailty in older adults with cancer and can help improve the identification of aging-related vulnerabilities. SMD from CT scans could be readily available to physicians treating older adults, and with improvement and further exploration of its utility, it may provide additional information before treatment courses and doses are selected. However, for now, this work reinforces the need to encourage alternative approaches for screening. Additionally, our work with geriatric assessment impairment classes can help physicians identify vulnerable patients through reduced geriatric assessments and can facilitate the planning of multiple support services for patients with clustered impairments who are starting cancer treatment. Overall, our work has implications for patient risk stratification which can inform future

interventions focused on maintaining older adults' physical function and quality of life through and after cancer treatment.

REFERENCES

1. Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. CA: A Cancer Journal for Clinicians. 2016;66(4):271-289. doi:doi:10.3322/caac.21349

2. Handforth C, Handforth C, Clegg A, Young C, Simpkins S. The prevalence and outcomes of frailty in older cancer patients: a systematic review. Annals of oncology. 2015;26(6):1091-1101. doi:10.1093/annonc/mdu540

3. Giri S, Al-Obaidi M, Weaver A, et al. Association Between Chronologic Age and Geriatric Assessment–Identified Impairments: Findings From the CARE Registry. Journal of the National Comprehensive Cancer Network. 2021;19(8):922-927.

4. Dale W, Williams GR, MacKenzie AR, et al. How Is Geriatric Assessment Used in Clinical Practice for Older Adults With Cancer? A Survey of Cancer Providers by the American Society of Clinical Oncology. JCO Oncology Practice. 17(6):336-344. doi:10.1200/op.20.00442

5. Mohile SG, Dale W, Somerfield MR, et al. Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2018;36(22):2326-2347. doi:10.1200/JCO.2018.78.8687

6. Williams GR, Kenzik KM, Parman M, et al. Integrating geriatric assessment into routine gastrointestinal (GI) consultation: The Cancer and Aging Resilience Evaluation (CARE). Journal of Geriatric Oncology. 2020;11(2):270-273. doi:10.1016/j.jgo.2019.04.008

7. Giri S, Mir N, Al-Obaidi M, et al. Use of Single-Item Self-Rated Health Measure to Identify Frailty and Geriatric Assessment-Identified Impairments Among Older Adults with Cancer. The oncologist. 2022;27(1):e45-e52.

8. Rockwood K, Mitnitski A, Song X, Steen B, Skoog I. Long-Term Risks of Death and Institutionalization of Elderly People in Relation to Deficit Accumulation at Age 70. Journal of the American Geriatrics Society. 2006;54(6):975-979. doi:https://doi.org/10.1111/j.1532-5415.2006.00738.x

9. Mitnitski AB, Graham JE, Mogilner AJ, Rockwood K. Frailty, fitness and late-life mortality in relation to chronological and biological age. BMC geriatrics. 2002;2(1):1-8. doi:10.1186/1471-2318-2-1

10. Buckinx F, Rolland Y, Reginster J-Y, Ricour C, Petermans J, Bruyère O. Burden of frailty in the elderly population: perspectives for a public health challenge. Archives of Public Health. 2015;73(1):19.

11. Xue Q-L, Tian J, Fried LP, et al. Physical Frailty Assessment in Older Women: Can Simplification Be Achieved Without Loss of Syndrome Measurement Validity? American journal of epidemiology. 2016;183(11):1037-1044. doi:10.1093/aje/kwv272

12. Fried LP, Tangen CM, Walston J, et al. Frailty in Older Adults: Evidence for a Phenotype. The Journals of Gerontology: Series A. 2001;56(3):M146-M157. doi:10.1093/gerona/56.3.M146

13. Bandeen-Roche K, Xue Q-L, Ferrucci L, et al. Phenotype of frailty: characterization in the women's health and aging studies. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2006;61(3):262-266.

14. Fugate Woods N, LaCroix AZ, Gray SL, et al. Frailty: Emergence and Consequences in Women Aged 65 and Older in the Women's Health Initiative Observational Study. Journal of the American Geriatrics Society. 2005;53(8):1321-1330. doi:doi:10.1111/j.1532-5415.2005.53405.x

15. Puts MT, Monette J, Girre V, et al. Are frailty markers useful for predicting treatment toxicity and mortality in older newly diagnosed cancer patients? Results from a prospective pilot study. Critical reviews in oncology/hematology. 2011;78(2):138-149.

16. Shachar SS, Deal AM, Weinberg M, et al. Body Composition as a Predictor of Toxicity in Patients Receiving Anthracycline and Taxane–Based Chemotherapy for Early-Stage Breast Cancer. Clinical Cancer Research. 2017;23(14):3537-3543. doi:10.1158/1078-0432.Ccr-16-2266

17. Delmonico M, Harris T, Visser M, et al. Longitudinal study of muscle strength, quality, and adipose tissue infiltration. The American journal of clinical nutrition. 2009;90(6):1579-1585.

18. Walston J, Hadley EC, Ferrucci L, et al. Research Agenda for Frailty in Older Adults: Toward a Better Understanding of Physiology and Etiology: Summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. Journal of the American Geriatrics Society. 2006;54(6):991-1001. doi:10.1111/j.1532-5415.2006.00745.x

19. Fried L, Walston J. Frailty and failure to thrive. In: Hazzard W BJ, Halter JB et al., ed. Principles of Geriatric Medicine and Gerontology. 5th ed. McGraw-Hill; 2003:1487–1502.

20. Morley JE, Vellas B, Abellan van Kan G, et al. Frailty Consensus: A Call to Action. Journal of the American Medical Directors Association. 2013;14(6):392-397. doi:https://doi.org/10.1016/j.jamda.2013.03.022

21. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2005;173(5):489-495.

22. King DE, Xiang J, Pilkerton CS. Multimorbidity trends in United States adults, 1988–2014. The Journal of the American Board of Family Medicine. 2018;31(4):503-513.

23. Evans WJ. Skeletal muscle loss: cachexia, sarcopenia, and inactivity. The American Journal of Clinical Nutrition. 2010;91(4):1123S-1127S. doi:10.3945/ajcn.2010.28608A

24. Carmeli E. Frailty and Primary Sarcopenia: A Review. In: Pokorski M, ed. Clinical Research and Practice. Springer International Publishing; 2017:53-68.

25. Evans WJ. What is sarcopenia? The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 1995;50(Special Issue):5-8.

26. Evans WJ, Morley JE, Argilés J, et al. Cachexia: a new definition. Clinical nutrition. 2008;27(6):793-799.

27. Xu L, Zhang J, Shen S, et al. Association Between Body Composition and Frailty in Elder Inpatients. Clinical interventions in aging. 2020;15:313-320. doi:10.2147/CIA.S243211

28. Soysal P, Stubbs B, Lucato P, et al. Inflammation and frailty in the elderly: a systematic review and meta-analysis. Ageing research reviews. 2016;31:1-8.

29. Van Epps P, Oswald D, Higgins P, et al. Frailty has a stronger association with inflammation than age in older veterans. Immunity & Ageing. 2016;13(1):27.

30. Hubbard RE, O'Mahony MS, Savva GM, Calver BL, Woodhouse KW. Inflammation and frailty measures in older people. Journal of cellular and molecular medicine. 2009;13(9b):3103-3109.

31. Bandeen-Roche K, Seplaki CL, Huang J, et al. Frailty in Older Adults: A Nationally Representative Profile in the United States. The journals of gerontology Series A,

Biological sciences and medical sciences. 2015;70(11):1427-1434. doi:10.1093/gerona/glv133

32. Clough-Gorr KM, Stuck AE, Thwin SS, Silliman RA. Older breast cancer survivors: geriatric assessment domains are associated with poor tolerance of treatment adverse effects and predict mortality over 7 years of follow-up. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28(3):380-386. doi:10.1200/JCO.2009.23.5440

33. Kristjansson SR, Nesbakken A, Jordhøy MS, et al. Comprehensive geriatric assessment can predict complications in elderly patients after elective surgery for colorectal cancer: A prospective observational cohort study. Critical reviews in oncology/hematology. 2010;76(3):208-217. doi:https://doi.org/10.1016/j.critrevonc.2009.11.002

34. Lee YH, Oh H-K, Kim D-W, et al. Use of a Comprehensive Geriatric Assessment to Predict Short-Term Postoperative Outcome in Elderly Patients With Colorectal Cancer. Annals of coloproctology. 2016;32(5):161-169. doi:10.3393/ac.2016.32.5.161

35. Ruiz J, Miller AA, Tooze JA, et al. Frailty assessment predicts toxicity during first cycle chemotherapy for advanced lung cancer regardless of chronologic age. Journal of Geriatric Oncology. 2019;10(1):48-54. doi:https://doi.org/10.1016/j.jgo.2018.06.007

36. Feliu J, Jiménez-Munárriz B, Basterretxea L, et al. Predicting Chemotherapy Toxicity in Older Patients with Cancer: A Multicenter Prospective Study. The Oncologist. 2020;

37. Wildiers H, Heeren P, Puts M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2014;32(24):2595-2603. doi:10.1200/JCO.2013.54.8347

38. Elsawy B, Higgins KE. The geriatric assessment. American family physician. 2011;83(1):48-56.

39. Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with cancer. Journal of Clinical Oncology. 2007;25(14):1824-1831.

40. Jolly TA, Deal AM, Nyrop KA, et al. Geriatric assessment-identified deficits in older cancer patients with normal performance status. The oncologist. 2015;20(4):379-385. doi:10.1634/theoncologist.2014-0247

41. Hurria A, Gupta S, Zauderer M, et al. Developing a cancer-specific geriatric assessment. Cancer. 2005;104(9):1998-2005. doi:10.1002/cncr.21422

42. Loh KP, Soto-Perez-de-Celis E, Hsu T, et al. What every oncologist should know about geriatric assessment for older patients with cancer: young international society of geriatric oncology position paper. Journal of oncology practice. 2018;14(2):85-94.

43. Williams GR. Geriatric assessment: precision medicine for older adults with cancer. Journal of oncology practice. 2018;14(2):97-98.

44. Cuthbertson CC, Kucharska-Newton A, Faurot KR, et al. Controlling for frailty in pharmacoepidemiologic studies of older adults: validation of an existing medicare claims-based algorithm. Epidemiology (Cambridge, Mass). 2018;29(4):556.

45. Hurria A, Gupta S, Zauderer M, et al. Developing a cancer-specific geriatric assessment: A feasibility study. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2005;104(9):1998-2005.

46. Williams GR, Rier HN, McDonald A, Shachar SS. Sarcopenia & aging in cancer. Journal of Geriatric Oncology. 2019;10(3):374-377. doi:https://doi.org/10.1016/j.jgo.2018.10.009

47. Aleixo GFP, Shachar SS, Nyrop KA, Muss HB, Malpica L, Williams GR. Myosteatosis and prognosis in cancer: Systematic review and meta-analysis. Critical reviews in oncology/hematology. 2020;145:102839. doi:https://doi.org/10.1016/j.critrevonc.2019.102839

48. Moon SW, Choi JS, Lee SH, et al. Thoracic skeletal muscle quantification: low muscle mass is related with worse prognosis in idiopathic pulmonary fibrosis patients. Respiratory Research. 2019;20(1):35. doi:10.1186/s12931-019-1001-6

49. Williams GR, Deal AM, Muss HB, et al. Frailty and skeletal muscle in older adults with cancer. J Geriatr Oncol. Jan 2018;9(1):68-73. doi:10.1016/j.jgo.2017.08.002

50. Zoico E, Corzato F, Bambace C, et al. Myosteatosis and myofibrosis: relationship with aging, inflammation and insulin resistance. Archives of gerontology and geriatrics. Nov-Dec 2013;57(3):411-416. doi:10.1016/j.archger.2013.06.001

51. Miljkovic I, Zmuda JM. Epidemiology of myosteatosis. Current opinion in clinical nutrition and metabolic care. May 2010;13(3):260-4. doi:10.1097/MCO.0b013e328337d826

52. Visser M, Goodpaster BH, Kritchevsky SB, et al. Muscle mass, muscle strength, and muscle fat infiltration as predictors of incident mobility limitations in well-functioning older persons. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2005;60(3):324-333.

53. Goodpaster BH, Carlson CL, Visser M, et al. Attenuation of skeletal muscle and strength in the elderly: The Health ABC Study. Journal of applied physiology. 2001;90(6):2157-2165.

54. Williams GR, Deal AM, Muss HB, et al. Skeletal muscle measures and physical function in older adults with cancer: sarcopenia or myopenia? Oncotarget. May 16 2017;8(20):33658-33665. doi:10.18632/oncotarget.16866

55. Fujiwara N, Nakagawa H, Kudo Y, et al. Sarcopenia, intramuscular fat deposition, and visceral adiposity independently predict the outcomes of hepatocellular carcinoma. Journal of hepatology. 2015;63(1):131-140.

56. Balducci L, Extermann M. Management of Cancer in the Older Person: A Practical Approach. The Oncologist. 2000;5(3):224-237. doi:10.1634/theoncologist.5-3-224

57. Droz J-P, Balducci L, Bolla M, et al. Management of prostate cancer in older men: recommendations of a working group of the International Society of Geriatric Oncology. BJU international. 2010;106(4):462-469. doi:10.1111/j.1464-410X.2010.09334.x

58. Ferrat E, Audureau E, Paillaud E, et al. Four Distinct Health Profiles in Older Patients With Cancer: Latent Class Analysis of the Prospective ELCAPA Cohort. The Journals of Gerontology: Series A. 2016;71(12):1653-1660. doi:10.1093/gerona/glw052

59. Menke A, Casagrande S, Geiss L, Cowie CC. Prevalence of and Trends in Diabetes Among Adults in the United States, 1988-2012. JAMA. 2015;314(10):1021-1029. doi:10.1001/jama.2015.10029

60. Lin CC, Virgo KS, Robbins AS, Jemal A, Ward EM. Comparison of Comorbid Medical Conditions in the National Cancer Database and the SEER–Medicare Database. Annals of surgical oncology. 2016;23(13):4139-4148. doi:10.1245/s10434-016-5508-5

61. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American journal of clinical oncology. 1982;5(6):649-656.

62. Beumer JH, Chu E, Salamone SJ. Body-Surface Area–Based Chemotherapy Dosing: Appropriate in the 21st Century? Journal of Clinical Oncology. 2012;30(31):3896-3897. doi:10.1200/jco.2012.44.2863

63. Du DB, Du EB. A formula to estimate the approximate surface area if height and weight be known. 1916. 1989.

64. Griggs JJ, Mangu PB, Temin S, Lyman GH. Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology clinical practice guideline. Journal of oncology practice. 2012;8(4):e59.

65. Baker SD, Verweij J, Rowinsky EK, et al. Role of Body Surface Area in Dosing of Investigational Anticancer Agents in Adults, 1991–2001. JNCI: Journal of the National Cancer Institute. 2002;94(24):1883-1888. doi:10.1093/jnci/94.24.1883

66. Felici A, Verweij J, Sparreboom A. Dosing strategies for anticancer drugs: the good, the bad and body-surface area. European journal of cancer. 2002;38(13):1677-1684.

67. de Jonge ME, Huitema ADR, Schellens JHM, Rodenhuis S, Beijnen JH. Individualised Cancer Chemotherapy: Strategies and Performance of Prospective Studies on Therapeutic Drug Monitoring with Dose Adaptation. journal article. Clinical pharmacokinetics. 2005;44(2):147-173. doi:10.2165/00003088-200544020-00002

68. Rudek MA, Sparreboom A, Garrett-Mayer ES, et al. Factors affecting pharmacokinetic variability following doxorubicin and docetaxel-based therapy. European Journal of Cancer. 2004;40(8):1170-1178. doi:https://doi.org/10.1016/j.ejca.2003.12.026

69. Saif MW, Choma A, Salamone SJ, Chu E. Pharmacokinetically Guided Dose Adjustment of 5-Fluorouracil: A Rational Approach to Improving Therapeutic Outcomes. JNCI: Journal of the National Cancer Institute. 2009;101(22):1543-1552. doi:10.1093/jnci/djp328

70. Morley JE, Malmstrom TK, Rodriguez-Mañas L, Sinclair AJ. Frailty, Sarcopenia and Diabetes. Journal of the American Medical Directors Association. 2014;15(12):853-859. doi:https://doi.org/10.1016/j.jamda.2014.10.001

71. Kalyani RR, Tian J, Xue QL, et al. Hyperglycemia and incidence of frailty and lower extremity mobility limitations in older women. Journal of the American Geriatrics Society. 2012;60(9):1701-1707.

72. Wu JH, Haan MN, Liang J, Ghosh D, et al. Diabetes as a predictor of change in functional status among older Mexican Americans: A population-based cohort study. Diabetes Care. 2003;26(2):314-9.

73. Astrom MJ, von Bonsdorff MB, Perala MM, et al. Glucose regulation and physical performance among older people: the Helsinki Birth Cohort Study. Acta diabetologica. Oct 2018;55(10):1051-1058. doi:10.1007/s00592-018-1192-1

74. Gregg EW, Mangione CM, Cauley JA, Thompson TJ, et al. Diabetes and incidence of functional disability in older women. Diabetes Care. 2002;25(1):61-7.

75. Park SW, Goodpaster BH, Strotmeyer ES, et al. Accelerated loss of skeletal muscle strength in older adults with type 2 diabetes: The Health, Aging and Body Composition Study. Diabetes care. 2007;30(6):1507-12

76. Lee CG, Schwartz AV, Yaffe K, et al. Changes in physical performance in older women according to presence and treatment of diabetes mellitus. Journal of the American Geriatrics Society. 2013;61(11):1872-1878.

77. Volpato S, Ferrucci L, Blaum C, Oster G, et al. Progression of lower-extremity disability in older women with diabetes: The Women's Health and Aging Study. Diabetes Care. 2003;26(1):70-5.

78. Kalyani RR, Kim C, Ferrucci L, et al. Sex differences in the association of fasting and postchallenge glucose levels with grip strength among older adults: the Rancho Bernardo Study. BMJ open diabetes research & care. 2015;3(1):e000086. doi:10.1136/bmjdrc-2015-000086

79. Kalyani RR, Metter EJ, Egan J, Golden SH, Ferrucci L. Hyperglycemia predicts persistently lower muscle strength with aging. Diabetes Care. Jan 2015;38(1):82-90. doi:10.2337/dc14-1166

80. Park SW, Goodpaster BH, Lee JS, et al. Excessive loss of skeletal muscle mass in older adults with type 2 diabetes. Diabetes Care. Nov 2009;32(11):1993-7. doi:10.2337/dc09-0264

81. Lee CG, Boyko EJ, Strotmeyer ES, et al. Association between insulin resistance and lean mass loss and fat mass gain in older men without diabetes mellitus. J Am Geriatr Soc. Jul 2011;59(7):1217-24. doi:10.1111/j.1532-5415.2011.03472.x

82. Lee JS, Auyeung TW, Leung J, Kwok T, Leung PC, Woo J. The effect of diabetes mellitus on age-associated lean mass loss in 3153 older adults. Diabetic medicine: a journal of the British Diabetic Association. Dec 2010;27(12):1366-71. doi:10.1111/j.1464-5491.2010.03118.x

83. Aghili R, Malek M, Valojerdi AE, Banazadeh Z, Najafi L, Khamseh ME. Body composition in adults with newly diagnosed type 2 diabetes: effects of metformin. Journal of diabetes and metabolic disorders. 2014;13(1):88. doi:10.1186/s40200-014-0088-z

84. Wang H, Ni Y, Yang S, Li H, Li X, Feng B. The effects of gliclazide, metformin, and acarbose on body composition in patients with newly diagnosed type 2 diabetes mellitus. Current therapeutic research, clinical and experimental. Dec 2013;75:88-92. doi:10.1016/j.curtheres.2013.10.002

85. Pan D, Lillioja S, Kriketos A, et al. Skeletal muscle triglyceride levels are inversely related to insulin action. Diabetes. 1997;46(6):983-988.

86. Simoneau J, Colberg S, Thaete FL, Kelley D. Skeletal muscle glycolytic and oxidative enzyme capacities are determinants of insulin sensitivity and muscle composition in obese women. The FASEB Journal. 1995;9(2):273-278.

87. Petersen KF, Befroy D, Dufour S, et al. Mitochondrial dysfunction in the elderly: possible role in insulin resistance. Science. 2003;300(5622):1140-1142.

88. Pritchard JM, Karampatos S, Beattie KA, et al. The relationship between intramuscular adipose tissue, functional mobility, and strength in postmenopausal women with and without type 2 diabetes. Journal of aging research. 2015;2015:872726

89. Goodpaster BH, Thaete FL, Simoneau J-A, Kelley DE. Subcutaneous abdominal fat and thigh muscle composition predict insulin sensitivity independently of visceral fat. Diabetes. 1997;46(10):1579-1585.

90. Goodpaster BH, Thaete FL, Kelley DE. Thigh adipose tissue distribution is associated with insulin resistance in obesity and in type 2 diabetes mellitus. Am J Clin Nutr. Apr 2000;71(4):885-92. doi:10.1093/ajcn/71.4.885

91. Miljkovic I, Cauley JA, Wang PY, et al. Abdominal myosteatosis is independently associated with hyperinsulinemia and insulin resistance among older men without diabetes. Obesity (Silver Spring, Md). Oct 2013;21(10):2118-25. doi:10.1002/oby.20346

92. Albu JB, Kovera AJ, Allen L, et al. Independent association of insulin resistance with larger amounts of intermuscular adipose tissue and a greater acute insulin response to glucose in African American than in white nondiabetic women. The American Journal of Clinical Nutrition. 2005;82(6):1210-1217.

93. Kaibori M, Ishizaki M, Iida H, et al. Effect of intramuscular adipose tissue content on prognosis in patients undergoing hepatocellular carcinoma resection. Journal of Gastrointestinal Surgery. 2015;19(7):1315-1323.

94. Van Rijssen L, van Huijgevoort N, Coelen R, et al. Skeletal muscle quality is associated with worse survival after pancreatoduodenectomy for periampullary, nonpancreatic cancer. Annals of surgical oncology. 2017;24(1):272-280.

95. Stretch C, Aubin J-M, Mickiewicz B, et al. Sarcopenia and myosteatosis are accompanied by distinct biological profiles in patients with pancreatic and periampullary adenocarcinomas. PloS one. 2018;13(5):e0196235.

96. Xiao J, Caan BJ, Weltzien E, et al. Associations of pre-existing co-morbidities with skeletal muscle mass and radiodensity in patients with non-metastatic colorectal cancer. Journal of cachexia, sarcopenia and muscle. 2018;9(4):654-663.

97. Xiao J, Caan BJ, Weltzien E, et al. Associations of pre-existing co-morbidities with skeletal muscle mass and radiodensity in patients with non-metastatic colorectal cancer. J Cachexia Sarcopenia Muscle. Aug 2018;9(4):654-663. doi:10.1002/jcsm.12301

98. Stretch C, Aubin JM, Mickiewicz B, et al. Sarcopenia and myosteatosis are accompanied by distinct biological profiles in patients with pancreatic and periampullary adenocarcinomas. PloS one. 2018;13(5):e0196235. doi:10.1371/journal.pone.0196235

99. Williams GR, Al-Obaidi M, Rower J, et al. Does oxaliplatin pharmacokinetics (PKs) explain associations between body composition and chemotherapy toxicity risk in older adults with gastrointestinal (GI) cancers? Journal of Clinical Oncology. 2021;39(15_suppl):3095-3095. doi:10.1200/JCO.2021.39.15_suppl.3095

100. Brehm A, Krssak M, Schmid AI, Nowotny P, Waldhäusl W, Roden M. Increased lipid availability impairs insulin-stimulated ATP synthesis in human skeletal muscle. Diabetes. 2006;55(1):136-140.

101. Shulman GI. Cellular mechanisms of insulin resistance. The Journal of clinical investigation. 2000;106(2):171-176. doi:10.1172/JCI10583

102. Lowell BB, Shulman GI. Mitochondrial dysfunction and type 2 diabetes. Science. 2005;307(5708):384-387.

103. Winter A, MacAdams J, Chevalier S. Normal protein anabolic response to hyperaminoacidemia in insulin-resistant patients with lung cancer cachexia. Clinical Nutrition. 2012;31(5):765-773. doi:https://doi.org/10.1016/j.clnu.2012.05.003

104. Trestini I, Gkountakos A, Carbognin L, et al. Muscle derangement and alteration of the nutritional machinery in NSCLC. Critical reviews in oncology/hematology. 2019;141:43-53.

105. Vettor R, Milan G, Franzin C, et al. The origin of intermuscular adipose tissue and its pathophysiological implications. American Journal of Physiology-Endocrinology and Metabolism. 2009;297(5):E987-E998. doi:10.1152/ajpendo.00229.2009

106. Lee D-E, Kehlenbrink S, Lee H, Hawkins M, Yudkin JS. Getting the message across: mechanisms of physiological cross talk by adipose tissue. American Journal of Physiology-Endocrinology and Metabolism. 2009;296(6):E1210-E1229. doi:10.1152/ajpendo.00015.2009

107. Rubenstein LZ, Stuck AE, Siu AL, Wieland D. Impacts of Geriatric Evaluation and Management Programs on Defined Outcomes: Overview of the Evidence. Journal of the American Geriatrics Society. 1991;39(S1):8S-16S. doi:10.1111/j.1532-5415.1991.tb05927.x

108. Ma D, Chow V, Popuri K, Beg MF. Comprehensive Validation of Automated Whole Body Skeletal Muscle, Adipose Tissue, and Bone Segmentation from 3D CT images for Body Composition Analysis: Towards Extended Body Composition. arXiv preprint arXiv:210600652. 2021.

109. Goodpaster BH, Kelley DE, Thaete FL, He J, Ross R. Skeletal muscle attenuation determined by computed tomography is associated with skeletal muscle lipid content. Journal of Applied Physiology. 2000;89(1):104-110. doi:10.1152/jappl.2000.89.1.104

110. Martin L, Birdsell L, MacDonald N, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. Journal of clinical oncology. 2013;31(12):1539-1547.

111. Martin L, Hopkins J, Malietzis G, et al. Assessment of computed tomography (CT)-defined muscle and adipose tissue features in relation to short-term outcomes after elective surgery for colorectal cancer: a multicenter approach. Annals of surgical oncology. 2018;25(9):2669-2680.

112. Mitnitski A, Song X, Skoog I, et al. Relative fitness and frailty of elderly men and women in developed countries and their relationship with mortality. Journal of the American Geriatrics Society. 2005;53(12):2184-2189.

113. Guerard EJ, Deal AM, Chang Y, et al. Frailty Index Developed From a Cancer-Specific Geriatric Assessment and the Association With Mortality Among Older Adults With Cancer. Journal of the National Comprehensive Cancer Network: JNCCN. Jul 2017;15(7):894-902. doi:10.6004/jnccn.2017.0122

114. Obaidi MA, Giri S, Mir N, et al. Use of self-rated health to identify frailty and predict mortality in older adults with cancer. Results from the care study. Journal of Clinical Oncology. 2020;38(15_suppl):12046-12046. doi:10.1200/JCO.2020.38.15_suppl.12046

115. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. BMC geriatrics. 2008;8(1):24. doi:10.1186/1471-2318-8-24

116. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA: a cancer journal for clinicians. Jan 2021;71(1):7-33. doi:10.3322/caac.21654

117. Cook NR. Statistical evaluation of prognostic versus diagnostic models: beyond the ROC curve. Clinical chemistry. 2008;54(1):17-23.

118. Pepe MS, Janes H, Longton G, Leisenring W, Newcomb P. Limitations of the odds ratio in gauging the performance of a diagnostic, prognostic, or screening marker. American journal of epidemiology. 2004;159(9):882-890.

119. Chubak J, Pocobelli G, Weiss NS. Tradeoffs between accuracy measures for electronic health care data algorithms. Journal of Clinical Epidemiology. 2012;65(3):343-349.e2. doi:https://doi.org/10.1016/j.jclinepi.2011.09.002

120. Zou KH, O'Malley AJ, Mauri L. Receiver-operating characteristic analysis for evaluating diagnostic tests and predictive models. Circulation. 2007;115(5):654-657.

121. Deeks JJ, Altman DG. Diagnostic tests 4: likelihood ratios. Bmj. 2004;329(7458):168-169.

122. Guyatt G, Rennie D, Meade M, Cook D. Users' guides to the medical literature: a manual for evidence-based clinical practice. vol 706. AMA press Chicago; 2002.

123. Hagenaars JA, McCutcheon AL. Applied latent class analysis. Cambridge University Press; 2002.

124. Muthén B, Muthén LK. Integrating Person-Centered and Variable-Centered Analyses: Growth Mixture Modeling With Latent Trajectory Classes. Alcoholism: Clinical and Experimental Research. 2000;24(6):882-891. doi:https://doi.org/10.1111/j.1530-0277.2000.tb02070.x

125. Weller BE, Bowen NK, Faubert SJ. Latent class analysis: a guide to best practice. Journal of Black Psychology. 2020;46(4):287-311.

126. Lanza ST, Rhoades BL. Latent class analysis: an alternative perspective on subgroup analysis in prevention and treatment. Prevention science. 2013;14(2):157-168.

127. Ethun CG, Bilen MA, Jani AB, Maithel SK, Ogan K, Master VA. Frailty and cancer: Implications for oncology surgery, medical oncology, and radiation oncology. CA: A Cancer Journal for Clinicians. 2017;67(5):362-377. doi:https://doi.org/10.3322/caac.21406

128. Lega IC, Lipscombe LL. Review: Diabetes, Obesity, and Cancer—Pathophysiology and Clinical Implications. Endocrine reviews. 2019;41(1):33-52. doi:10.1210/endrev/bnz014

129. Ling S, Brown K, Miksza JK, et al. Risk of cancer incidence and mortality associated with diabetes: A systematic review with trend analysis of 203 cohorts. Nutrition, Metabolism and Cardiovascular Diseases. 2021;31(1):14-22. doi:https://doi.org/10.1016/j.numecd.2020.09.023

130. Correa-de-Araujo R, Addison O, Miljkovic I, et al. Myosteatosis in the context of skeletal muscle function deficit: an interdisciplinary workshop at the National Institute on Aging. Frontiers in physiology. 2020:963.

131. Williams GR, Mackenzie A, Magnuson A, et al. Comorbidity in older adults with cancer. Journal of geriatric oncology. Jul 2016;7(4):249-57. doi:10.1016/j.jgo.2015.12.002

132. Fillenbaum GG. Multidimensional functional assessment of older adults: The Duke Older Americans Resources and Services procedures. Psychology Press; 2013.

133. Williams GR, Deal AM, Lund JL, et al. Patient-reported comorbidity and survival in older adults with cancer. The oncologist. 2018;23(4):433-439.

134. Roth WD. The multiple dimensions of race. Ethnic and Racial Studies. 2016;39(8):1310-1338.

135. Caleyachetty R, Barber TM, Mohammed NI, et al. Ethnicity-specific BMI cutoffs for obesity based on type 2 diabetes risk in England: a population-based cohort study. The Lancet Diabetes & Endocrinology. 2021;9(7):419-426. doi:10.1016/S2213-8587(21)00088-7

136. Williams GR, Deal AM, Sanoff HK, et al. Frailty and health-related quality of life in older women with breast cancer. Support Care Cancer. Jul 2019;27(7):2693-2698. doi:10.1007/s00520-018-4558-6

137. Altman DG, Bland JM. Interaction revisited: the difference between two estimates. Bmj. 2003;326(7382):219.

138. Pritchard JM, Karampatos S, Beattie KA, et al. The Relationship between Intramuscular Adipose Tissue, Functional Mobility, and Strength in Postmenopausal Women with and without Type 2 Diabetes. Journal of aging research. 2015;2015:872726. doi:10.1155/2015/872726

139. Bellera C, Rainfray M, Mathoulin-Pelissier S, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. Annals of Oncology. 2012;23(8):2166-2172.

140. Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. Journal of Clinical Oncology. 2011;29(25):3457.

141. Mei ZB, Zhang ZJ, Liu CY, et al. Survival benefits of metformin for colorectal cancer patients with diabetes: a systematic review and meta-analysis. PloS one. 2014;9(3):e91818. doi:10.1371/journal.pone.0091818

142. Muss HB, Woolf S, Berry D, et al. Adjuvant chemotherapy in older and younger women with lymph node–positive breast cancer. Jama. 2005;293(9):1073-1081.

143. Sargent DJ, Goldberg RM, Jacobson SD, et al. A Pooled Analysis of Adjuvant Chemotherapy for Resected Colon Cancer in Elderly Patients. New England Journal of Medicine. 2001;345(15):1091-1097. doi:10.1056/NEJMoa010957

144. Nadaraja S, Matzen L-E, Jørgensen TL, et al. The impact of comprehensive geriatric assessment for optimal treatment of older patients with cancer: A randomized parallel-group clinical trial. Journal of Geriatric Oncology. 2020;11(3):488-495.

145. Li D, Sun C-L, Kim H, et al. Geriatric Assessment–Driven Intervention (GAIN) on Chemotherapy-Related Toxic Effects in Older Adults With Cancer: A Randomized Clinical Trial. JAMA Oncology. 2021;7(11):e214158-e214158. doi:10.1001/jamaoncol.2021.4158

146. Pilleron S, Sarfati D, Janssen-Heijnen M, et al. Global cancer incidence in older adults, 2012 and 2035: A population-based study: Global cancer incidence in older adults. International journal of cancer. 2018;144. doi:10.1002/ijc.31664

147. Williams GR, Deal AM, Lund JL, et al. Patient-Reported Comorbidity and Survival in Older Adults with Cancer. The oncologist. Apr 2018;23(4):433-439. doi:10.1634/theoncologist.2017-0404

148. Sherbourne CD, Stewart AL. The MOS social support survey. Social science & medicine. 1991;32(6):705-714.

149. Pergolotti M, Lyons KD, Williams GR. Moving beyond symptom management towards cancer rehabilitation for older adults: Answering the 5W's. Journal of Geriatric Oncology. 2018;9(6):543-549. doi:https://doi.org/10.1016/j.jgo.2017.11.009

150. Pergolotti M, Deal AM, Lavery J, Reeve BB, Muss HB. The prevalence of potentially modifiable functional deficits and the subsequent use of occupational and physical therapy by older adults with cancer. J Geriatr Oncol. May 2015;6(3):194-201. doi:10.1016/j.jgo.2015.01.004

151. Winters-Stone KM, Horak F, Jacobs PG, et al. Falls, Functioning, and Disability Among Women With Persistent Symptoms of Chemotherapy-Induced Peripheral Neuropathy. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2017;35(23):2604-2612. doi:10.1200/jco.2016.71.3552

152. Harrington SE, Stout NL, Hile E, et al. Cancer rehabilitation publications (2008–2018) with a focus on physical function: a scoping review. Physical therapy. 2020;100(3):363-415.

153. Kleckner AS, Magnuson A. The nutritional needs of older cancer survivors. Journal of Geriatric Oncology. 2022;13(5):738-741. doi:10.1016/j.jgo.2021.12.007

154. Kadambi S, Soto-Perez-de-Celis E, Garg T, et al. Social support for older adults with cancer: Young International Society of Geriatric Oncology review paper. Journal of geriatric oncology. 2020;11(2):217-224.

155. Koll T, Pergolotti M, Holmes HM, et al. Supportive Care in Older Adults with Cancer: Across the Continuum. Current oncology reports. Aug 2016;18(8):51. doi:10.1007/s11912-016-0535-8

156. Fann JR, Fan MY, Unützer J. Improving primary care for older adults with cancer and depression. Journal of general internal medicine. Nov 2009;24 Suppl 2(Suppl 2):S417-24. doi:10.1007/s11606-009-0999-4

157. Stubblefield MD. Cancer rehabilitation: principles and practice. Springer Publishing Company; 2018.

158. Singh H, Kanapuru B, Smith C, et al. FDA analysis of enrollment of older adults in clinical trials for cancer drug registration: a 10-year experience by the US Food and Drug Administration. American Society of Clinical Oncology; 2017. 35:15_suppl: 10009.